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The American Journal of Medicine

VOL. VI JUNE, 1949 NO. 6

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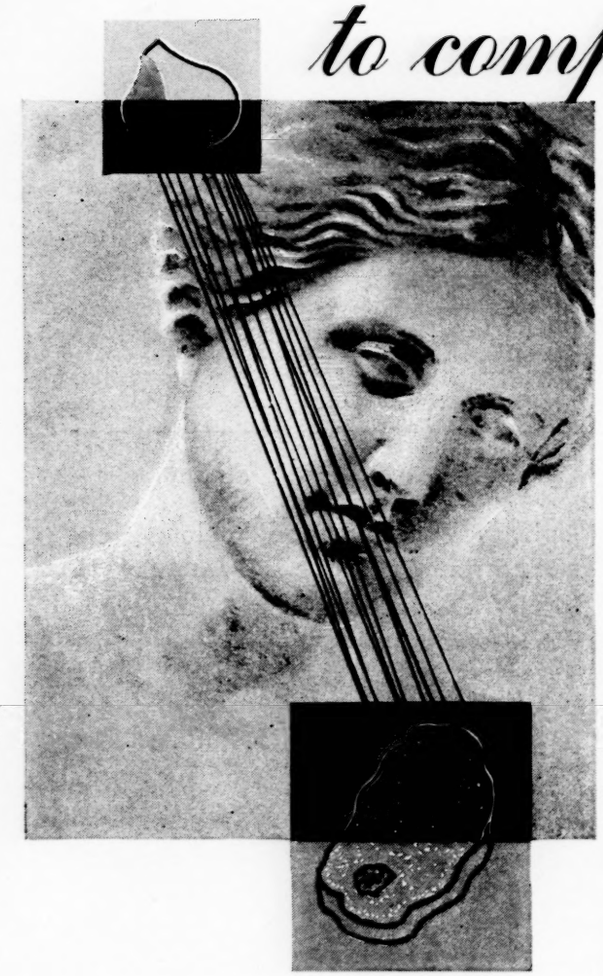

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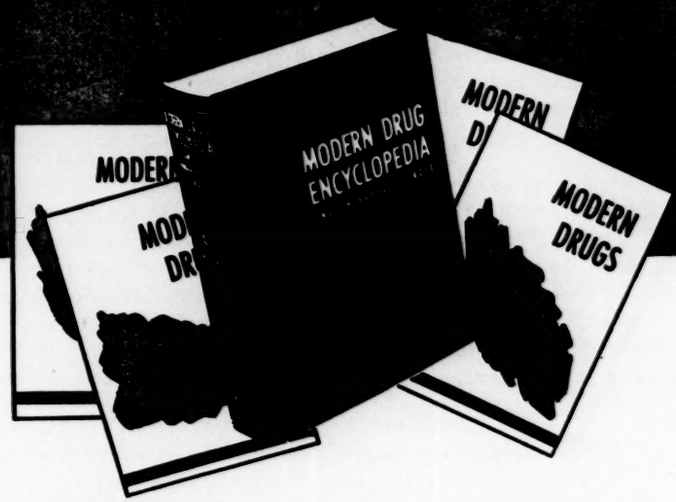

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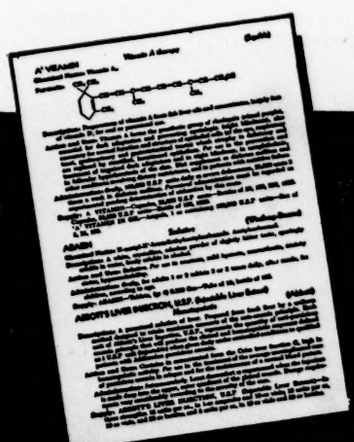

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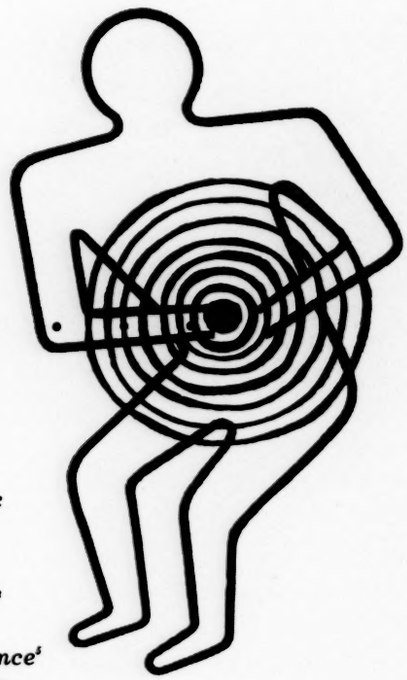

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[1] Malyoth, G.: Klin. Wchnschr. *13*:51, 1934.
[2] Bittner, J. E., Jr.: Northwest Med. *35*:445 (Dec.) 1936.
[3] Myers, P. B., and Rouse, A. H.: Am. J. Digest. Dis. *7*:39 (Jan.) 1940.
[4] Powers, J. L.: Bull. National Formulary Committee *9*:5 (Oct.) 1940.
[5] Block, L. H., Tarnowski, A., and Green, B. L.: Am. J. Digest. Dis. *6*:96 (Apr.) 1939.
[6] Morrison, L. M.: Am. J. Digest. Dis. *13*:196 (June) 1946.

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*Spies, T. D.; Suarez, R. M.; Lopez, G. G.; Milanes, F.; Stone, R. E.; Toca, R. L.; Aramburu, T., and Kartus, S.: Tentative Appraisal of Vitamin B_{12} as a Therapeutic Agent, J.A.M.A. *139*:521 (Feb. 19) 1949.

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(1) *Original paper prepared by E. B. Carpenter, M. D., Department of Orthopedic Surgery, Medical College of Virginia Hospital, Richmond, Va.*

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"The cases chosen for this investigation were carefully selected from a busy orthopedic service in a prominent teaching hospital. The cases selected were in each instance chosen by the writer and followed personally throughout their course of treatment and follow-up . . .

"The period covered in this clinical study was nine months: (See: "Follow-up Observations" for final conclusions); 127 cases were selected and treated during this period . . .

"The chlorophyll preparations* used were: (1) water-soluble active chlorophyll derivatives in isotonic solution; (2) water-soluble chlorophyll derivatives in a hydrophylic ointment base; (3) chlorophyll-penicillin solution containing 2,000 units of penicillin per cc. of water-soluble chlorophyll derivatives; (4) fine mesh gauze impregnated with water-soluble chlorophyll derivative ointment.

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Results in 25 cases of subacute or chronic suppurative osteomyelitis secondary to compound fractures

". . . skin defects were covered and the wounds healed in twenty-three instances. The two other wounds broke down following skin grafting and required additional skin grafting or plastic closures . . .

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*The water soluble chlorophyll derivative preparations used in this study were generously supplied by Rystan Company, Inc., Mt. Vernon, N. Y., and are marketed commercially under the trade name "Chloresium."

Results in 22 cases of chronic granulomatous wounds

"The group of chronic granulomatous lesions not associated with underlying bony infection consisted principally of decubitus ulcers. Nine such ulcers were on paraplegic patients and the results here were most gratifying. Early erradication of gross infection, early appearance of healthy granulation and progressive epithelization of these decubiti were marked in every instance. Every patient selected in this group had been treated previously with various local ointments and solutions with uniformly poor results . . . Of the total group of twenty-two cases, failure to obtain healing occurred in six instances.

Results in 6 cases of chronic varicose ulcers

". . . diminution in the size of the ulcer occurred in every instance within two weeks and complete epithelization was obtained in four instances . . . in each case selected very definite improvement occurred with chlorophyll ointment although previously the ulcers had been resistant to all types of treatment.

CONCLUSIONS

"In the treatment of chronic suppurative osteomyelitis, both of hematogenous origin and secondary to compound fractures, the efficacy of chlorophyll solution locally combined with adequate sequestrectomy, produced uniformly rapid erradication of infection, early wound healing and substantial evidence of clinical cures, not previously experienced in this type of infection when treated by the usual time-honored methods of sequestration . . .

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"The period of follow-up has not been less than eighteen months for any case and on a number of cases two years of observation have been possible.

"In the group of patients with chronic suppurative osteomyelitis, of whom fifty-four originally healed following sequestrectomy and delayed primary closure, two have developed recurrence of infection requiring additional surgery . . . The remaining patients have been clinically asymptomatic with no evidence of recurrence of infection...

"The group of cases of osteomyelitis following compound fractures has been very interesting to observe. Of this original group of twenty-four patients, additional surgery has been necessary in six . . . Of the entire group of eighteen patients who have not required additional surgery there has been no evidence of recurrence of infection . . .

"The group of indolent ulcers or decubiti, particularly on paraplegics, have remained healed without evidence of breakdown.

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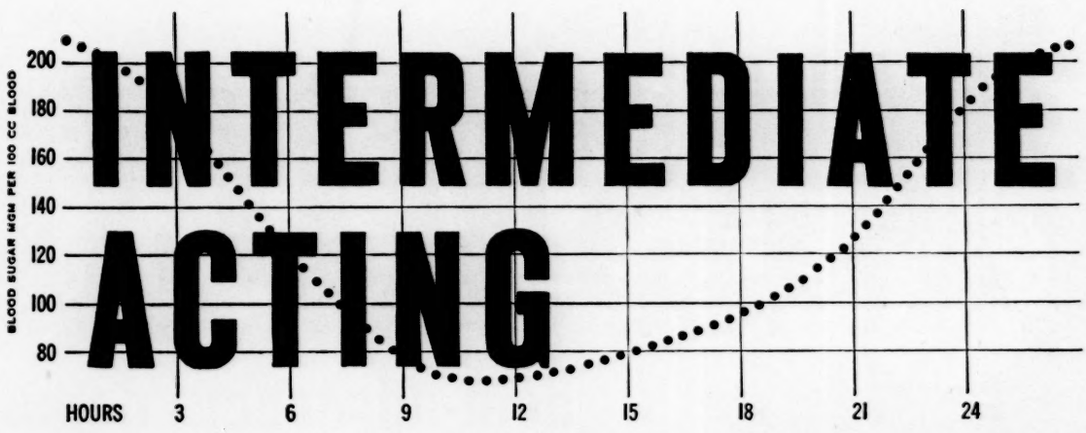
*Philpott, N. W., Hendelman, M., and Primrose, T. Methionine in Obstetrics, Am. Jr. Obst. & Gynec. 57:125-142 Jan. 1949



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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetic Assn. 8:37, 1948.

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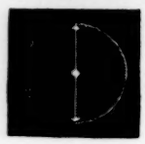

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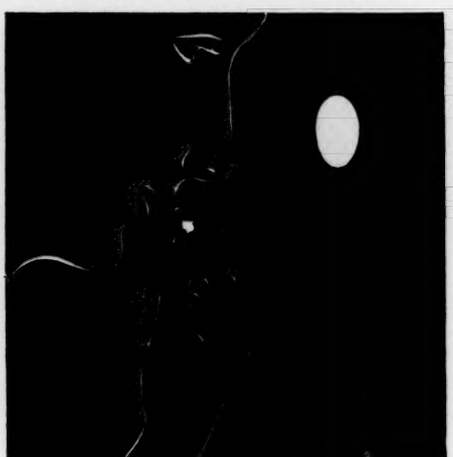

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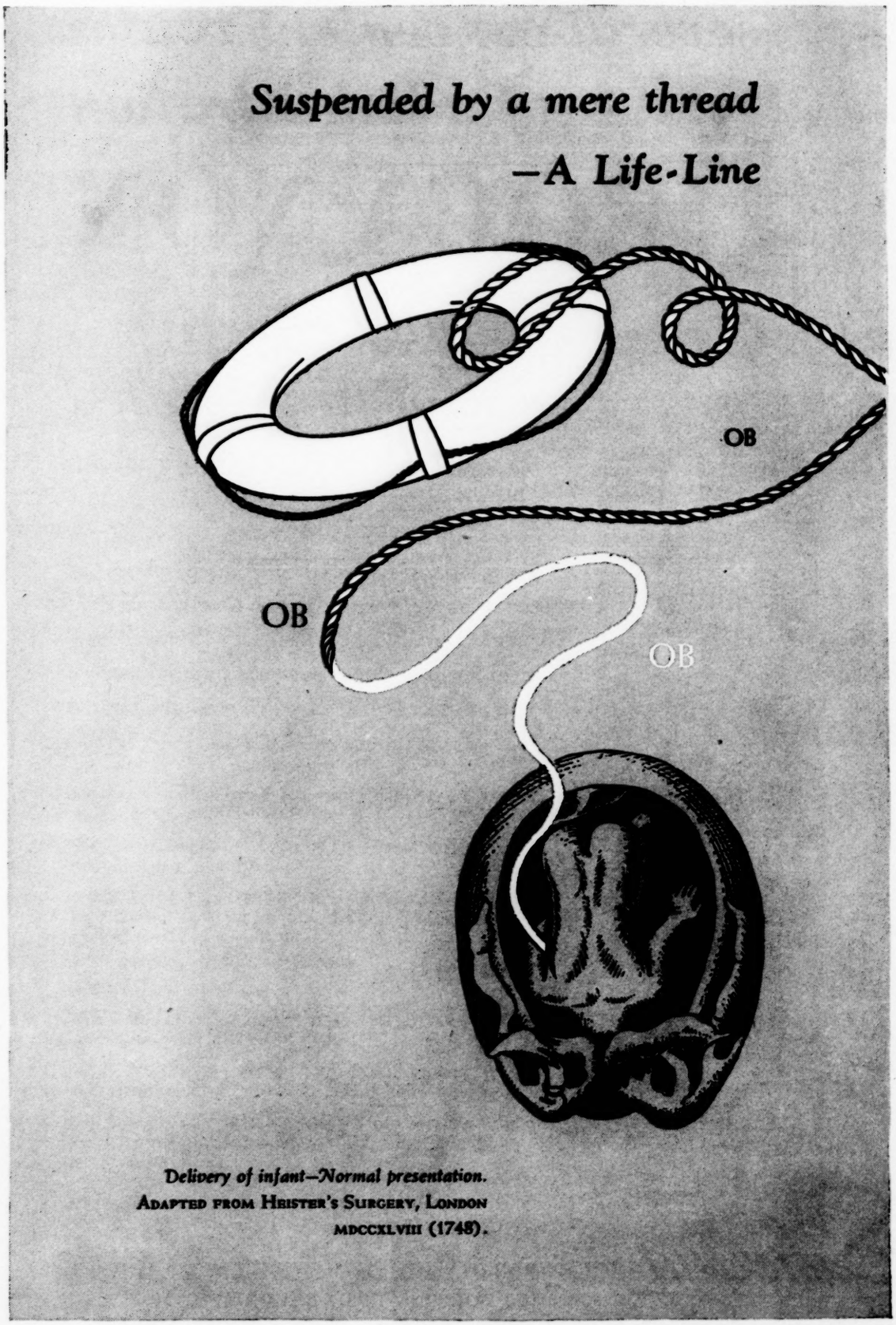

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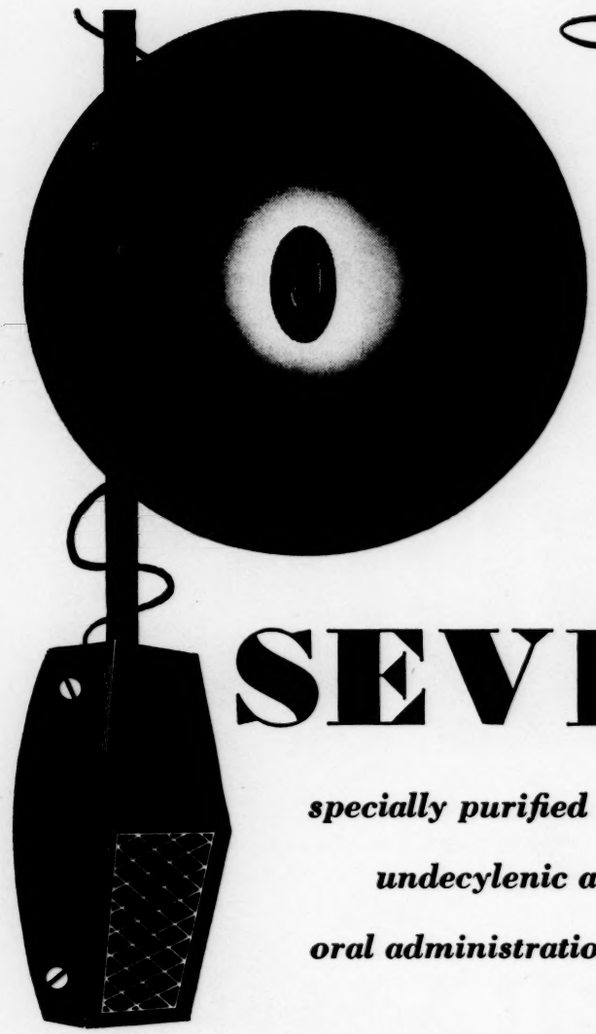

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1. Undecylenic Acid and Psoriasis, editorial, J.A.M.A. 139:460, 1949.
2. Perlman, H. H.: J.A.M.A. 139:444, 1949.

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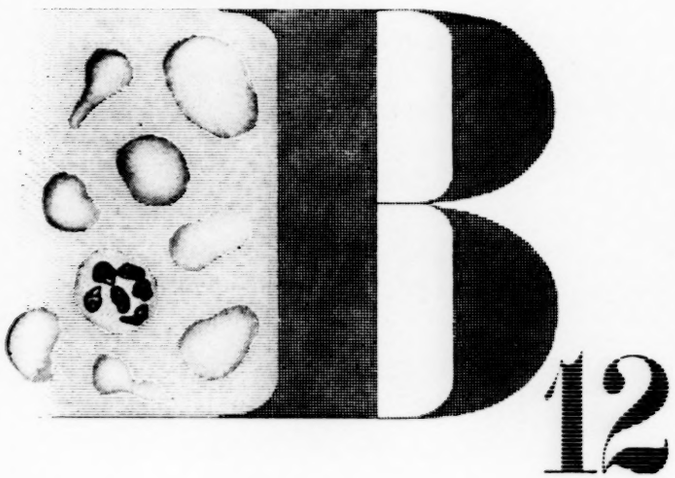

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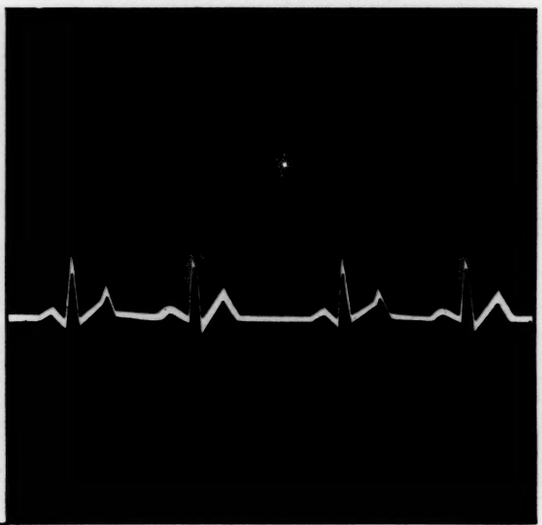

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The American Journal of Medicine

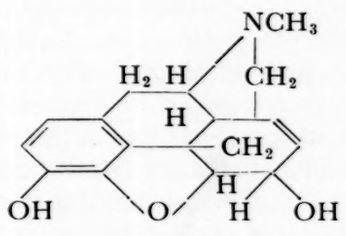
VOL. VI JUNE, 1949 No. 6

Editorial

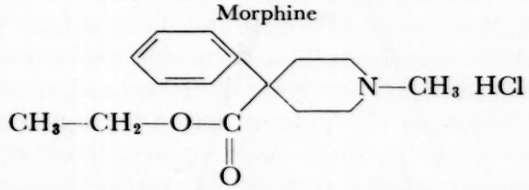
Synthetic Analgesic Drugs

FEW drugs have as impressive a history as opium. It has been used for more than two millenia although its important therapeutic applications were not generally recognized until more recently. The isolation of the principal alkaloids of opium in the nineteenth century and the more recent chemical modification of alkaloidal structure to produce substances such as dihydromorphinone (Dilaudid) and methyldihydromorphinone (metopon) represented important steps forward but did not foretell great progress in the search for analgesic drugs which could replace morphine or its related alkaloids.

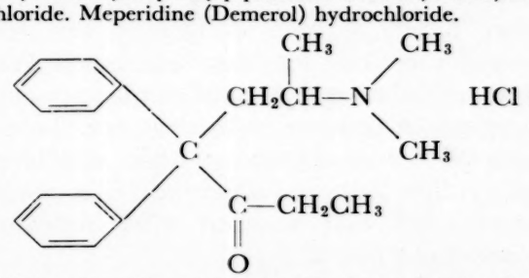
Only a decade has passed since the announcement of Eisleb and Schaumann that a relatively simple compound, meperidine (Demerol, Dolantin), an ester of phenylpiperidinecarboxylic acid, is a potent analgesic drug. This discovery proved that the structural peculiarities of the alkaloids of the morphine group need not dominate the search for new analgesics. It promised new insight into the relationship between chemical structure on the one hand, and analgesic potency, undesired toxic effects and addiction-liability on the other. This promise has been strengthened by the recent introduction of methadone. Methadone (amidon, Dolophine, Adanon) is a synthetic analgesic as potent as morphine. A derivative of heptanone, its structure differs from that of meperidine. The formulas here given enable one to compare the structures of morphine, meperidine and methadone.



Morphine



Ethyl-l-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. Meperidine (Demerol) hydrochloride.



6-Dimethyl-amino-4,4-diphenyl-heptanone-3 hydrochloride. Methadone (Dolophine, Adanon) hydrochloride.

Drugs used for a specific effect often have similar patterns of action extending to effects which either are undesired or undesirable or both. How similar are the pharmacologic patterns of morphine, meperidine and methadone? All three relieve pain and the analgesic action is the primary therapeutic use to which they are put. Meperidine is about one-tenth as potent as the other two in terms of the dose required for analgesia. Specialized experimental algesimetric tests suggested that methadone is even more

potent than morphine. However, clinical comparisons have not consistently revealed important differences in dose and for practical purposes morphine and methadone can be regarded as equipotent analgesics.

Is the liability to addiction with physical dependence and tolerance-development necessarily a part of the pharmacologic pattern of a potent analgesic drug? The evidence available requires an affirmative answer to this question although that answer must be provisional and subject to qualification. Himmelsbach, Isbell and their colleagues have studied in addicts as quantitatively as possible the phenomena of addiction to morphine and of physical dependence on the drug as measured by signs and symptoms of withdrawal. The addiction-liability of morphine with the development of unusual tolerance is notoriously high and there is a correspondingly great physical dependence on the drug. If morphine be used as a standard of addiction, then meperidine can be considered an analgesic of low addiction-liability. Primary habituation and addiction to meperidine have occurred but the number of such cases in psychiatrically normal persons is certainly small. On the other hand, it is a dangerous but less desired substitute for morphine in the real or potential morphine-addict and appears to resemble codeine in this respect. Tolerance of the analgesic or toxic effects of meperidine appears slowly and is much lower than that reached after repeated doses of morphine.

Apart from its analgesic action, the best evidence that methadone is a pharmacologic relative of morphine comes from studies of its effects in addicts. It can provide a euphoria nearly as satisfying as that of morphine and Anslinger has warned that addicts are often successful in obtaining the drug from physicians who would be suspicious of a request for morphine. It can be substituted for morphine without recognition by the addict. In fact, its substitution for morphine followed by abrupt withdrawal is probably the best means of withdrawing morphine since the abstinence syndrome after methadone is much milder than after morphine alone (Isbell and others). Therefore, physical dependence, measured by abstinence symptoms, is much lower than for morphine even after doses of methadone approaching the limits of tolerance. If one were limited only to these considerations, he might conclude that the addiction-liability of methadone is considerable. Such a generalization may approach the truth in the real or potential addict but at present cannot be sustained from clinical experience in normal patients. There has been no report of primary addiction to methadone. In experimental animals, especially dogs, varying degrees of addiction with tolerance have been produced. On the other hand, in the monkey from which any data obtained should be more significant, Seevers and his colleagues could demonstrate addiction and tolerance-development for morphine but not for methadone. Normal patients requiring a drug for the relief of severe pain have taken methadone for weeks or even months. Tolerance may or may not appear and require a moderate increase of dose. Primary addiction with withdrawal symptoms has not been reported.

It would be expected that habituation and addiction would be facilitated by an analgesic causing euphoria. The euphoria which is commonly observed in patients receiving therapeutic doses of morphine occurs infrequently after meperidine (less than 10 per cent of patients) and perhaps even less often after methadone. Sedation is unquestionably much more pronounced after morphine than after meperidine or methadone. Indeed, the sedative action of methadone is usually so slight as to make it less suitable than morphine for special uses such as pre-anesthetic medication from which sedation may be desired. Cough can be efficiently suppressed by small doses of methadone whereas after meperidine an antitussive effect is not observed. The effects of the three drugs on smooth muscle offer interesting similarities and contrasts. Morphine reduces the propulsive activity of the

gastrointestinal tract by complex effects; it causes smooth muscle spasm especially of the sphincters; it lessens the secretion of digestive glands; its central action interferes with the defecation reflex. Although thought to be a spasmolytic drug, meperidine in normal persons usually increases smooth muscle tone, particularly of the small intestine. Neither meperidine nor methadone causes constipation. The spasmogenic action of meperidine is also illustrated by its action on the sphincter of the common bile duct which is thrown into spasm so that the intrabiliary pressure rises. Morphine and codeine act similarly. Morphine causes ureteral spasm whereas the effect of meperidine, if any, is to relax the smooth muscle of the ureters. At least in the anesthetized dog the injection of methadone is followed by relaxation of the ureters.

A comparison of the toxic effects of doses in the therapeutic range does not favor morphine. Dizziness, nausea and vomiting may follow the administration of any of the three analgesics. The frequency of these signs and symptoms, especially reported in ambulatory patients, is probably as high after morphine as after either meperidine or methadone. Minor toxic symptoms may be more characteristic of a particular drug. For example, pruritus is more common after morphine; flushing, perspiration and dryness of the mouth are more frequent after meperidine. Lethal doses of any of the three drugs cause respiratory paralysis. However, effects of therapeutic doses on respiration can usually be demonstrated only after morphine. Exceptional are patients with intracranial lesions in whom meperidine may cause an alarming respiratory depression. In contrast, meperidine is the best available potent analgesic for obstetric use. Unlike either morphine or methadone it does not cause serious depression of respiration in the newborn infant. Toxic doses of all three analgesics cause mixed signs of central depression and excitation. Diffuse excitation rather than depression is more characteristic of meperidine than of morphine or methadone.

A comparison of morphine with its synthetic competitors, meperidine and methadone, demonstrates that either or both substitutes can usually replace it as a powerful and reasonably specific analgesic. The discovery of these synthetic analgesics, differing in structure from each other and from morphine, has greatly stimulated the investigation of related compounds, some of which have remarkable pharmacologic properties which are not necessarily desirable therapeutically. The therapeutic value of meperidine and methadone justifies an unrelenting search for better analgesics which may also be found, by trial and error, in compounds not suspected of possessing analgesic properties. Perhaps the ideal analgesic drug, specific for the relief of pain, useful for long periods without increase of dose or danger of habituation or addiction and causing few or trivial toxic effects can be discovered.

H. B. VAN DYKE, M.D.
Columbia University College
of Physicians and Surgeons,
New York, N. Y.

Clinical Studies

Modification of the Effects of Immobilization upon Metabolic and Physiologic Functions of Normal Men by the Use of an Oscillating Bed*

G. Donald Whedon, M.D., John E. Deitrick, M.D. *and* Ephraim Shorr, M.D.
with the technical assistance of
V. Toscani, V. Buniak Davis *and* E. Stevens
New York, New York

The effect of immobilization upon various metabolic and physiologic functions of four normal young men has been the subject of a previous communication.[1] The results of this study revealed that immobilization over periods of several weeks brought about significant losses of nitrogen, sulfur, calcium, phosphorus and potassium in healthy men. Creatine metabolism, control of the circulation in the upright position, and muscle mass and strength were also significantly impaired. These findings provided a quantitative measure of the degree to which immobilization *per se* may contribute to the metabolic and circulatory derangements observed in traumatic and infectious states.

There has been a rapidly growing interest in recent years in the development of methods for shortening convalescence. These methods have included early ambulation for postoperative patients[2–5] and programs of physical reconditioning inaugurated during the war by the British[6] and later adopted by our own military forces.[7–10] These methods are not generally applicable to all disease states or to all types of patients; they are primarily designed for convalescence after brief illness and for patients whose physical condition is such as to permit ambulant activity during convalescence. All these programs allow for a variable period of inactivity after the infectious, surgical or traumatic episode prior to the institution of rehabilitating procedures

The present study was primarily concerned with the development of procedures which could be instituted without delay and which would be applicable to conditions necessitating prolonged immobilization and for which convalescent training methods are unsuitable. These represent an important group of diseases, such as spinal cord injury, fracture of the pelvis or spine, severe burns and abdominal wounds, and extensive paralysis resulting from poliomyelitis or cerebral vascular accidents. Prolonged immobilization exposes these patients not only to derangements of circulatory, muscular and metabolic functions but also to the dangers of stone formation in the urinary tract and its consequences. The

* From the Department of Medicine, Cornell University Medical College, the New York Hospital and the Russell Sage Institute of Pathology, New York, N. Y. This investigation was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College, and was aided in part by a grant from the National Foundation for Infantile Paralysis, Inc.

desirability of any procedure which would maintain the body in the best possible metabolic and physiologic state during the period of enforced immobilization is evident.

Among the methods considered were calisthenic exercises, massage and passive exercise. These were quite unsuitable for the specific experimental conditions being explored which required that the lower half of the subjects' bodies be encased in plaster, as in the previous study, which was to serve as the base-line for the evaluation of the therapeutic regimen. The extent of the circulatory derangements observed during immobilization in the previous study suggested that benefit might be derived from any device, such as the oscillating bed described by Sanders[11] which would bring about continuous postural changes. It was conceivable that this bed, which rocks slowly back and forth, raising the head and lowering the feet with each oscillation, might exert favorable effects upon the circulation and possibly upon metabolic functions. This bed had the further advantage of being applicable to patients immobilized in plaster. Finally, any gain achieved by use of the bed would conserve nursing and physiotherapy facilities. For these reasons, the Sanders oscillating bed was selected for evaluation of its possible beneficial effects on the variety of physiologic and metabolic effects previously observed to follow immobilization in an ordinary hospital or fixed bed.

PROCEDURE

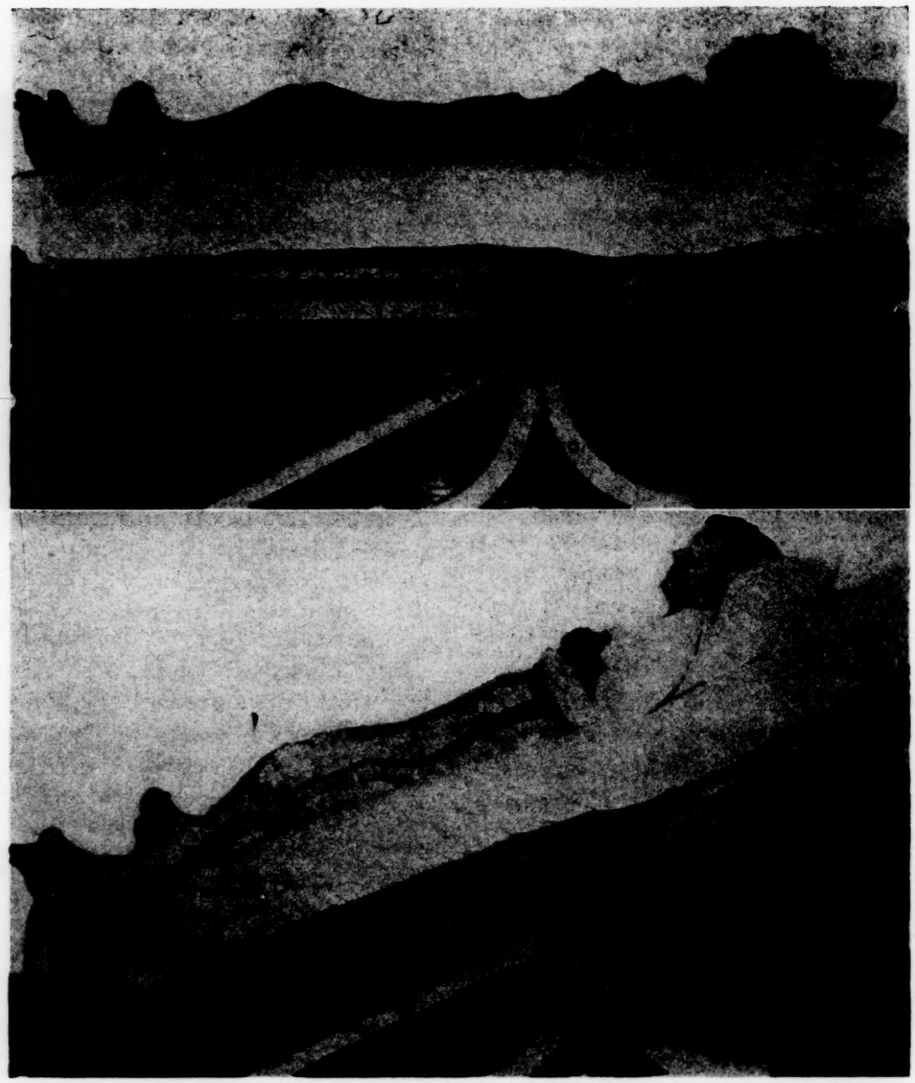
Three normal healthy young men were studied on a constant dietary intake before, during and following a five-week period of immobilization in plaster casts in oscillating beds. The three subjects had all taken part in the immobilization experiment (on standard hospital or fixed beds) previously reported.[1] The metabolic and physiologic data of each subject in the fixed bed experiment could therefore serve as the control for his data in the present experiment since the same experimental conditions were maintained, except for the use of oscillating beds during the immobilization period. Identical metabolic balances and physiologic studies were carried out on the Metabolism Ward of the New York Hospital and the Russell Sage Institute of Pathology.

During the control phase of the experiment, which lasted four to five and one-half weeks, the subjects carried on the same degree of activity as in the control phase of the fixed bed experiment. In addition to being up and about on the Metabolism Ward, they took exercise in the form of calisthenics for one-half hour, swimming for one-half hour each day and one hour walks outside the hospital under escort three or four times a week.

During the immobilization period, which lasted five weeks, the subjects were placed in the same type of cast as in the fixed bed experiment, a bivalved plaster cast extending from the umbilicus to the toes. Time out of the casts for bowel movements and for tilt table and ergometer tests was the same as in the fixed bed experiment and averaged thirty to forty minutes daily.

For subjects E. M. and C. O. the oscillating bed was in motion altogether eight hours daily. For subject S. W. the oscillating bed was in motion twenty-one hours daily, being stopped only for meals, bed baths and bowel movements. The beds rocked slowly up and down on a fulcrum at the middle of the bed (Figs. 1 and 2); the total arc of excursion was 24 degrees, the feet moving 5 degrees above and 19 degrees below the horizontal. The speed of oscillation was adjusted so that one complete cycle required one and three-fourths minutes. The subjects became adjusted to the motion of the bed within two days. The bed rocked so slowly that they were barely conscious of movement and were merely aware of a slight shift of weight with each oscillation and slight pressure chiefly on the bottom of the heels in the foot-down position. The pressure on the heels initially provoked some soreness and redness which was eliminated by adjustment of the padding of the cast.

During the recovery period the subjects were allowed to be progressively ambulant on the third day and by the twelfth day resumed the same level of activity as during the control period. In subjects E. M. and C. O. recovery was studied for five weeks. In S. W. recovery was studied for six and one-half weeks following which he was again immobilized for a two-week period, this time in a *fixed* bed. The re-immobilization of this subject in a fixed bed was carried



FIGS. 1 and 2. Subject in bi-valved plaster cast on oscillating bed, showing arc of excursion employed. One complete cycle required one and three-fourths minutes. Figure 1, head of bed down 5 degrees. Figure 2, foot of bed down 19 degrees.

out for the purpose of providing a check on the results of the first fixed bed experiment. Would the same healthy young individual respond to immobilization in a fixed bed in the same way and to the same degree as he had one year previously? The recovery phase following the two weeks' re-immobilization of S. W. was studied for eleven days.

Subjects E. M. and C. O. were studied in the oscillating bed experiment from September to December, 1945, during the same months of the year but one year later than they had been studied in the fixed bed experiment. Subject S. W. was studied from February to January, 1946, exactly one year after he had been studied in the fixed bed experiment.

SUBJECTS

The subjects, E. M., C. O. and S. W., ranging in age from twenty-one to thirty years, were described in the report of the fixed bed experiment.[1] The subjects' heights and weights are shown in Table I.

DIETS

Throughout the experiment all three subjects received a 2,800 calorie diet, the composition of which is given in Table I. In the previous fixed

bed experiment C. O. and S. W. had received this same diet whereas E. M. had received a diet of slightly lower caloric (2,500) and mineral content. A description of the diets and of their composition as determined by direct analyses were given in the previous study[1] and in greater detail in separate reports.[12,13] Sodium intake was kept constant at 4.0 Gm. per day for all subjects in this experiment. In S. W. the slight increase in nitrogen, calcium and phosphorus intake beginning at period VIII occurred because of the necessity for using the wartime "emergency" bread made from dark flour.*

TABLE I

DAILY DIETARY INTAKE AND PHYSICAL CHARACTERISTICS OF SUBJECTS

Subject	Age Yr.	Height Cm.	Weight Kg.	Calories	Protein Gm.	Fat Gm.	CHO Gm.	Ca Gm.	P Gm.	Na Gm.	K Gm.
E. M.	30	177	72	2800	90	114	352	0.920	1.64	4.00	3.76
C. O.	21	180	66	2800	90	114	352	0.920	1.64	4.00	3.76
S. W.	21	181	66	2800	90	114	352	0.920	1.64	4.00	3.76

METHODS

A. Chemical Studies. The metabolic balances (in seven-day periods), collection and preparation of specimens and methods of chemical analyses were carried out in the same manner as in the fixed bed experiment.[1] Urinary calcium, phosphorus and citric acid[14] were determined on consecutive four- and three-day pooled specimens.

B. Physiologic Studies. Physiologic studies were carried out as described in the report of the fixed bed experiment with the following modifications. In all subjects, measurements of the girth of the legs were made with the device previously described[1] which involves the use of a wide metal band encircling the leg under constant and equal tension. With this device measurements of the circumference of the calves could be closely checked by different observers (standard deviation for four control weeks among all subjects = ± 2.4 mm., or 0.67 per cent). Blood coagulation studies included the determination of coagulation time by the Lee-White method and prothrombin time by a modification of the method of Herbert; in addition, heparin tolerance tests as outlined by de Takats[15] and prothrombin time determinations by the Link-Shapiro method[16] were carried out on S. W.

* The authors are deeply indebted to Elizabeth Curtin, head nurse of the Metabolism Ward, for the supervision of the dietary and other aspects of the "patient" care during this and the previous immobilization study.

RESULTS

A. Chemical Studies. 1. Nitrogen: During the control periods the subjects maintained small positive nitrogen balances with the output relatively constant. The average of the total outputs of the last three control periods served as the control base-line. Displacements or variations from the control base-line were employed for the calculation of the total losses of nitrogen occurring during immobilization on the oscillating bed and in the single re-immobilization in the fixed bed (subject S. W.). Calculation of the total losses occurring during immobilization in the first fixed bed experiment, with which these losses will be compared, were made in the same manner.

During the first four days of immobilization there was little change in nitrogen output. A rise then occurred which began on the fifth or sixth day and reached its maximum during the second and third weeks. In comparison with the fixed bed experiment the pattern of nitrogen loss was similar but the extent of nitrogen loss was approximately one-half as great in two of the three subjects. In the third subject (C. O.), whose losses of nitrogen were small in both experiments, the loses were almost identical in both types of immobilization. The repetition of immobilization of subject S. W. in the fixed bed (for two weeks) resulted in a loss of nitrogen identical with

the loss sustained during the same period of time in the first fixed bed experiment and approximately twice as great as during the initial two weeks in the oscillating bed.

During the recovery phase the subjects promptly began to retain nitrogen. By the end of the third week of recovery E. M. had regained all of the nitrogen lost during immobilization and thereafter stored additional nitrogen. C. O. and S. W. regained nearly all of their lost nitrogen by the end of the fifth recovery week. Maximum retention of nitrogen occurred at the fifth week for E. M. and C. O., at the second week for S. W.

A more detailed comparison of the changes in nitrogen metabolism in the fixed and oscillating bed experiments is presented in Figure 3 and Tables II and III.

TABLE II

COMPARISON OF NITROGEN METABOLISM DURING AND FOLLOWING FIVE WEEKS' IMMOBILIZATION IN FIXED AND OSCILLATING BEDS*

I. IMMOBILIZATION

Subject	Control	Five-week Period of Immobilization						
							Maximum Deviation from Control Base-line	
	Average Daily Balance Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total N Loss, First 2 Weeks Gm.	Total N Loss, First 3 Weeks Gm.	Total N Loss, 5 Weeks Gm.	Week of Occurrence	Deviation Gm./day (for that week)
E. M., fixed	+1.36	−0.81	2.17	40.32	58.31	75.95	2nd	−3.55
E. M., oscillating	+0.61	−0.36	0.97	17.43	27.79	33.95	2nd	−2.26
C. O., fixed	+1.54	+0.86	0.68	10.29	16.66	23.80	3rd	−0.91
C. O., oscillating	+1.66	+0.95	0.71	8.05	15.61	24.85	3rd	−1.08
S. W., fixed	+0.60	−0.82	1.42	20.72	38.43	49.70	2nd	−2.78
S. W., oscillating	+1.55	+0.68	0.87	11.90	16.24	30.45	2nd	−1.69

II. RECOVERY

Subject	Average Daily Balance through First 4 Weeks Gm.	Average Daily Gain through First 4 Weeks Gm.	Total N Retention, First 3 Weeks Gm.	Total N Retention, First 4 Weeks Gm.	Total N Retention, First 5 Weeks Gm.	Total N Retention, 6 Weeks Gm.
E. M., fixed	+2.15	0.79	8.54	22.12		
E. M., oscillating	+2.41	1.80	37.03	50.40	66.22	
C. O., fixed	+2.18†	0.64†	13.44			
C. O., oscillating	+1.97†	0.31†	6.44	14.28	22.89	
S. W., fixed	+2.21	1.61	24.22	45.01	61.53	73.29
S. W., oscillating	+2.49	0.94	21.63	26.46	30.38	34.79

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance in oscillating bed experiment = average of last three control weeks.

† Data given for first three weeks, since in this subject in the fixed bed experiment balance studies were carried out only through the first three recovery weeks.

2. *Calcium:* During the control periods the subjects were approximately in calcium equilibrium. During immobilization there was a gradual increase in calcium excretion. This increase occurred principally in the

urine, the increase in fecal calcium being small and variable. Urinary calcium excretion increased less rapidly than in the fixed bed experiment, and by the third to fourth week reached a plateau-like peak which was substantially lower than the base-line excretion of each of the subjects was somewhat higher in the oscillating bed experiment, the rise in urinary calcium from the base-line and the total losses of calcium in the urine were considerably smaller during the immobilization in the

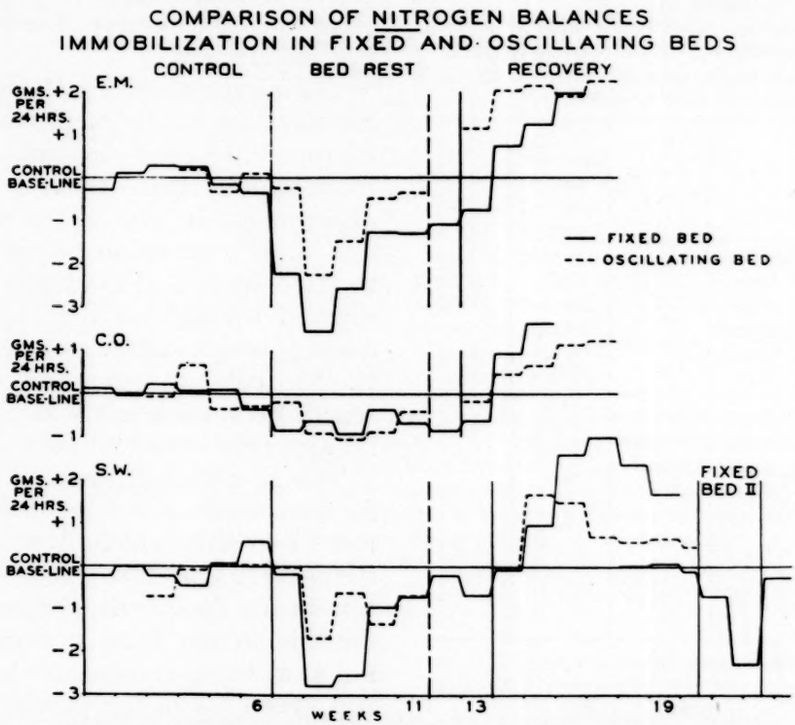


FIG. 3. Comparison of the changes in nitrogen metabolism resulting from immobilization in fixed and oscillating beds in three normal male subjects. The balances are plotted as deviations from the control baseline which in the fixed bed experiment was an average of the balances of the last four control weeks and in the oscillating bed experiment an average of the last three control weeks. In this and in each of the subsequent graphs "bed rest" indicates the immobilization phase of the experiments. The interrupted vertical line in the bed rest area of the graph marks the end of the five weeks during which the subjects were immobilized in oscillating beds; this convention has been adopted in each of the graphs in order to permit comparison of the metabolic and physiologic changes during an equal period of immobilization. "Fixed Bed II" refers to a two-week period of re-immobilization of subject S. W. in a fixed bed following recovery from immobilization in an oscillating bed.

levels reached during immobilization in the fixed bed. For all three subjects the maximal urinary calcium excretion (for a three- or four-day pooled specimen) ranged from 155 to 458 mg. per day with an average maximum of 311 mg. as contrasted with the maximum urinary calcium excretion of the same three subjects in the fixed bed, of 140 to 594 mg., with an average maximum of 362 mg. Since the control oscillating bed. (Table IV and Fig. 4.) The average maximum increase in urinary calcium in the oscillating bed experiment was 121 mg., in the fixed bed experiment 233 mg. The total losses of calcium in the *urine* during immobilization in the oscillating bed averaged only 51 per cent of the total losses for the same period of time during immobilization in the fixed bed. The total losses (urinary plus fecal) in the oscillating bed

experiment averaged 46 per cent of the total losses in the fixed bed experiment. (Table v and Fig. 5.)

Factors influencing urinary calcium solubility showed little or no change. Urine volumes increased slightly (average daily urine volumes averaged 250 cc. higher during the immobilization periods than during the control periods). Urinary pH rose between 0.1 and 0.2 units (the slight shift toward alkalinity being less favorable for calcium solubility). Citric acid excretion did not change significantly. These findings were the same as were observed in the fixed bed experiment.

During the recovery phase following immobilization in the oscillating bed calcium excretion receded toward control levels more rapidly than it did in the fixed bed experiment. In two of the subjects, C. O. and S. W., retention began at the second to third week and gradually became more marked throughout the five to six weeks during which recovery was studied. In E. M. calcium excretion approximately reached control levels at the third week but no appreciable calcium retention occurred.

The re-immobilization of subject S. W. for two weeks in a fixed bed resulted in a rise in urinary calcium at approximately the same rate as during his first immobilization in the fixed bed. The control base-line for this second fixed bed experiment was not at a closely comparable level to the control base-lines of the previous experiments

TABLE III

COMPARISON OF NITROGEN METABOLISM DURING A TWO WEEKS RE-IMMOBILIZATION IN FIXED BED WITH FIRST TWO WEEKS OF IMMOBILIZATION IN PREVIOUS FIXED AND OSCILLATING BED EXPERIMENTS

Experiment (Subject S. W.)	Control Base-line Balance Gm./day	Deviation of N Balance during 2nd Week from Control Base-line Gm./day (for the week)	Increase above Control Level of Average Daily Urinary N Output during 2nd Week Gm./day	Total N Loss during 2 Weeks Immobilization Gm.
Fixed bed I.....	+0.60	−2.78	2.77	20.72
Oscillating bed...	+1.55	−1.69	1.76	11.90
Fixed bed II.....	+2.11*	−2.27	2.05	20.72

* Control base-line balance of second fixed bed experiment = average of last three periods (18 days) of oscillating bed experiment recovery phase.

TABLE IV

COMPARISON OF URINARY CALCIUM EXCRETION DURING FIVE WEEKS IMMOBILIZATION IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					
	Control Base-line Urinary Calcium Output* Gm./day	Average Daily Urinary Calcium Output Gm.	Increase above Control Base-line of Average Daily Urinary Calcium Output Gm.	Total Urinary Calcium Loss Gm.	Maximum Urinary Calcium		
					Week of Occurrence	Maximum (for that week) Gm./day	Deviation from Control Base-line Gm./day
E. M., fixed.....	0.050	0.100	0.050	1.75	4th	0.119	0.069
E. M., oscillating	0.096	0.130	0.034	1.19	5th	0.149	0.053
C. O., fixed.....	0.116	0.274	0.158	5.53	5th	0.319	0.203
C. O., oscillating	0.223	0.284	0.061	2.13	3rd	0.306	0.083
S. W., fixed.....	0.213	0.494	0.281	9.84	5th	0.577	0.364
S. W., oscillating	0.252	0.382	0.130	4.55	5th	0.445	0.193

* Control base-line urinary calcium output in fixed bed experiment = average of last four control weeks; control base-line urinary calcium output in oscillating bed experiment = average of last three control weeks.

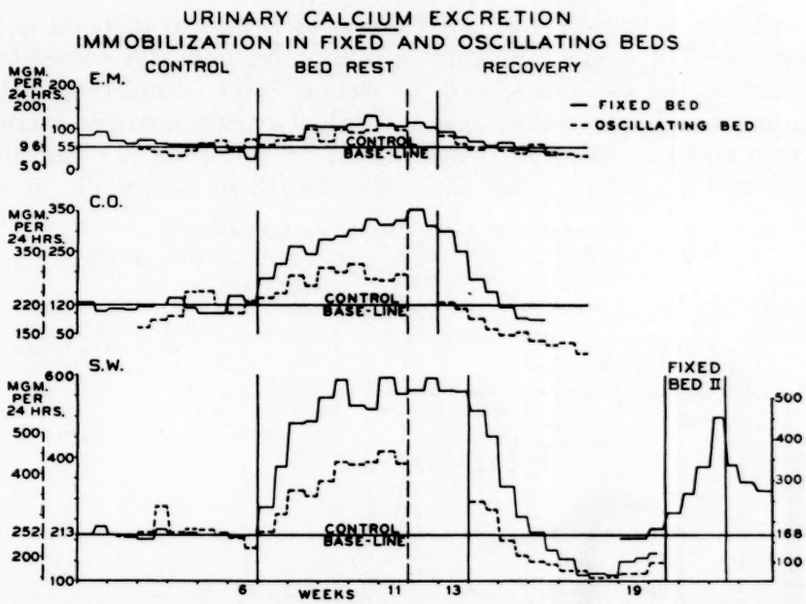


FIG. 4. Comparison of the changes in the urinary excretion of calcium resulting from immobilization in fixed and oscillating beds in three normal male subjects. The ordinate scales for urinary calcium excretion (in mg. per twenty-four hours) have been placed so that the control baselines of the fixed and oscillating bed experiments are superimposed. The control baseline urinary calcium excretion for the fixed bed experiment was an average of the outputs of the last four control weeks, for the oscillating bed experiment an average of the outputs of the last three control weeks; for the re-immobilization of subject S. W. in a fixed bed (Fixed Bed II) the control baseline was an average of the last two periods (eleven days) of the oscillating bed experiment recovery phase.

TABLE V

COMPARISON OF TOTAL CALCIUM METABOLISM DURING FIVE WEEKS' IMMOBILIZATION IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					Recovery Period		Total Calcium Deficit (A + B) Gm.
	Average Daily Balance* Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total Ca Loss during Immobilization (A) Gm.	Maximum Deviation from Control Base-line		No. of Weeks of Additional Calcium Loss	Total Additional Calcium Loss during Recovery (B) Gm.	
					Week of Occurrence	Deviation Gm./day (for that week)			
E. M., fixed.....	+0.131	−0.026	0.157	5.50	5th	−0.280	4	2.76	8.26
E. M., oscillating	+0.055	−0.024	0.079	2.76	5th	−0.175	2	1.37	4.13
C. O., fixed.....	+0.130	−0.108	0.238	8.33	5th	−0.329	3	2.04	10.37
C. O., oscillating	+0.010	−0.058	0.068	2.38	5th	−0.157	1	0.99	3.37
S. W., fixed.....	+0.081	−0.253	0.334	11.69	5th	−0.500	3	5.25	16.94
S. W., oscillating	+0.101	−0.098	0.199	6.96	4th	−0.278	2	1.39	8.35

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance in oscillating bed experiment = average of last three control weeks.

because some calcium retention was still going on six and one-half weeks following the immobilization in the oscillating bed. However, the prompt and marked increase in urinary calcium when S. W. was again placed in a fixed bed is evident. (Fig. 4.)

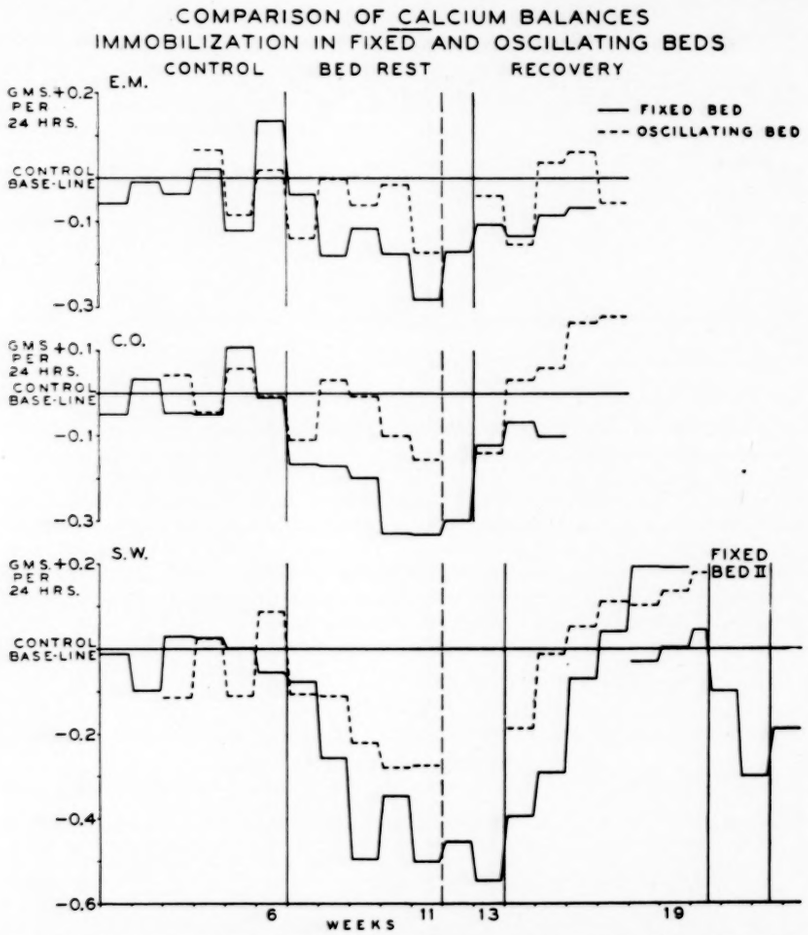


FIG. 5. Comparison of the changes in calcium metabolism resulting from immobilization in fixed and oscillating beds in three normal male subjects. The balances are plotted as deviations from the control baseline which in the fixed bed experiment was an average of the balances of the last four control weeks and in the oscillating bed experiment an average of the last three control weeks.

This increase was twice as great as occurred during the same length of time in the oscillating bed. (Table VI.)

3. *Phosphorus:* During the control phase the subjects maintained small positive balances as related to intake. During immobilization there was an increase in both urinary and fecal phosphorus excretion; the increase in fecal phosphorus, however, was very small and variable. Urinary phosphorus began to increase promptly during immobilization and reached a peak at the second week, coinciding closely with the peak of urinary nitrogen excretion. A second peak of phosphorus excretion occurred at the fourth to fifth weeks at the time when calcium excretion was at maximum levels. During recovery phosphorus excretion fell rapidly to levels below the control base-line, greatest retention of phosphorus occurring at the third to fourth recovery weeks.

The total amounts of phosphorus lost during the five weeks' immobilization in the oscillating bed were significantly less than resulted in the fixed bed in two of the three subjects. (Table VII.) In E. M. and C. O.

TABLE VI

COMPARISON OF URINARY AND TOTAL CALCIUM METABOLISM DURING TWO WEEKS' RE-IMMOBILIZATION IN FIXED BED WITH FIRST TWO WEEKS OF IMMOBILIZATION IN PREVIOUS FIXED AND OSCILLATING BED EXPERIMENTS

Experiment (Subject S. W.)	Control		Two-week Period of Immobilization					
	Control Base-line Urinary Calcium Output Gm./day	Control Base-line Balance Gm./day	Average Daily Urinary Calcium Output during 2nd Week Gm./day	Maximum Urinary Calcium		Total Urinary Calcium Loss Gm.	Deviation of Ca Balance of 2nd Week from Control Base-line Gm./day	Total Calcium Loss (Urinary plus Fecal) Gm.
				Maximum, Derived from a 3- or 4-day Pooled Urine Specimen (during 2nd week) Gm./day	Deviation from Control Base-line Gm./day			
Fixed bed I.....	0.213	+0.081	0.486	0.488	0.275	2.674	−0.255	2.317
Oscillating bed.	0.252	+0.101	0.355	0.361	0.109	0.910	−0.111	1.526
Fixed bed II....	0.168*	+0.235**	0.383	0.452	0.284	2.009	−0.300	2.786

* Control base-line urinary calcium output of second fixed bed experiment = average of last two periods (11 days) of oscillating bed experiment recovery phase.

** Control base-line balance of second fixed bed experiment = average of last three periods (18 days) of oscillating bed experiment recovery phase.

TABLE VII

COMPARISON OF PHOSPHORUS METABOLISM DURING FIVE WEEKS' IMMOBILIZATION IN FIXED AND OSCILLATING BEDS

Subject	Control	Five-week Period of Immobilization					
	Average Daily Balance* Gm.	Average Daily Balance Gm.	Average Daily Loss Gm.	Total Urinary Phosphorus Loss Gm.	Total Phosphorus Loss (Urinary Plus Fecal) Gm.	Maximum Deviation from Control Base-line	
						Week of Occurrence	Deviation Gm./day (for the week)
E. M., fixed.....	+0.328	+0.050	0.278	4.62	9.73	2nd	−0.373
						5th	−0.319
E. M., oscillating...	+0.151	+0.014	0.137	3.22	4.79	1st	−0.235
C. O., fixed.....	+0.278	+0.147	0.131	3.89	4.58	4th	−0.188
C. O., oscillating...	+0.191	+0.105	0.086	2.38	3.01	1st	−0.142
						4th	−0.103
S. W., fixed.....	+0.169	−0.046	0.215	7.49	7.53	3rd	−0.370
S. W., oscillating...	+0.189	−0.046	0.235	7.70	8.22	2nd	−0.256
						4th	−0.288

* Control base-line balance in fixed bed experiment = average of last four control weeks; control base-line balance of oscillating bed experiment = average of last three control weeks.

the losses of phosphorus in the *urine* during immobilization in the oscillating bed were 70 per cent and 61 per cent, respectively, of the amounts lost by these two subjects in the urine during immobilization in the fixed bed; the total losses (urinary plus fecal) were 49 per cent and 65 per cent, respectively, of the total amounts lost during immobilization in the fixed bed. In S. W. the total phosphorus loss (urinary plus fecal) during the five weeks' immobilization in the oscillating bed exceeded the total loss during five weeks in the fixed bed by 9 per cent. The amounts lost in the *urine* by this subject were nearly identical for five weeks' immobilization in both experiments; the amounts of phosphorus lost in the urine during the two weeks of re-immobilization in the fixed bed and during the first two weeks of immobilization in the oscillating bed and first fixed bed experiments were also nearly identical in this subject.

4. *Total sulfur:* The ratio of urinary total sulfur to urinary total nitrogen during the last three control weeks was 1:15.4 for E. M., 1:15.8 for C. O. and 1:15.2 for S. W. As in the fixed bed experiment, this sulfur:nitrogen ratio was maintained quite constantly from week to week throughout the immobilization and recovery period, suggesting a sulfur rich source for the excreted nitrogen, presumably muscle in large measure. (Table VIII.)

TABLE VIII

RATIO OF URINARY NITROGEN TO URINARY TOTAL SULFUR (OSCILLATING BED EXPERIMENT)

Periods	Subject E. M.			Subject C. O.			Subject S. W.		
	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio	Average Daily Urinary Nitrogen Gm.	Average Daily Urinary Total Sulfur Gm.	N:S Ratio
Control									
Last four weeks	14.09	0.912	15.44	11.30	0.683	16.55	11.94	0.783	15.26
	12.67	0.823	15.39	10.48	0.645	16.24	11.86	0.745	15.92
	12.95	0.826	15.68	11.93	0.759	15.73	11.29	0.755	14.96
	12.72	0.842	15.13	11.73	0.759	15.48	11.66	0.790	14.78
Average of last 3 control weeks	12.78	0.830	15.40	11.38	0.721	15.80	11.61	0.763	15.22
Immobilization									
1st week	12.57	0.797	15.78	11.64	0.740	15.74	11.56	0.770	15.03
2nd week	14.81	0.888	16.69	12.69	0.762	16.65	13.36	0.875	15.27
3rd week	14.27	0.884	16.13	12.85	0.778	16.52	12.55	0.848	14.80
4th week	13.34	0.883	15.12	12.34	0.775	15.93	13.15	0.840	15.66
5th week	13.04	0.845	15.44	11.70	0.757	15.48	12.51	0.835	14.99
Recovery									
1st week	11.77	0.765	15.39	11.35	0.705	16.10	11.93	0.788	15.14
2nd week	10.70	0.686	15.60	10.60	0.686	15.47	10.12	0.700	14.48
3rd week	10.79	0.733	14.73	10.37	0.693	14.97	10.37	0.680	15.26
4th week	10.92	0.735	14.88	10.03	0.688	14.60	11.29	0.753	15.00
5th week	10.06	0.692	14.56	9.91	0.680	14.60	11.36	0.755	15.06
6th week							11.30	0.773	14.62

5. *Potassium:* During the control phase the subjects were approximately in potassium equilibrium. During the first week or

first two weeks of immobilization potassium excretion increased in all three subjects. Thereafter there was wide variation among the subjects. In E. M. the excretion of potassium remained elevated throughout the immobilization period declining toward equilibrium during the last two weeks; his total loss of potassium was 7.63 Gm. In S. W. potassium was lost during the first three weeks of immobilization and retained during the last two weeks, yielding a net loss of 1.75 Gm. C. O. exhibited a marked potassium retention during the last three weeks of immobilization so that his overall balance for the five weeks was +6.3 Gm. In spite of these marked individual variations in potassium excretion, the balances of all three subjects were less negative during immobilization in the oscillating bed than during the same length of time in the fixed bed.

6. *Sodium:* During immobilization sodium excretion increased slightly. The increase occurred only in urinary excretion, fecal excretion remaining less than 0.04 Gm. daily during all phases of the experiment. The total losses of sodium ranged from 3.85 Gm. to 8.75 Gm. during five weeks' immobilization.

During recovery sodium excretion diminished to control levels. In two subjects sodium retention did not occur. In the third subject retention occurred only during the first two recovery weeks.

Sodium balance studies had been carried out in both the fixed and oscillating bed experiments in only one subject, S. W. In this subject the total sodium loss was 6.72 Gm. during five weeks in the fixed bed, 8.75 Gm. during five weeks in the oscillating bed.

7. *Creatine metabolism:* As in the fixed bed experiment, urinary creatinine excretion remained quite constant throughout all periods of study. Creatine excretion showed day to day fluctuations at a low level (dietary intake not creatine-free), but no significant shifts occurred from one phase of study to the next. However, the decreases in creatine tolerance occurring as a result of immobilization were significantly altered by the use of the oscillating bed. Although creatine tolerance also declined progressively during the immobilization stage of this experiment, the extent of decline was considerably less than during immobilization in the fixed bed experiment. (Table IX.) The lowest percentages of creatine retention in tests of creatine tolerance during immobilization in the oscillating bed were 81 per cent, 42 per cent and 64 per cent for E. M., C. O. and S. W., respectively. During the same period of immobilization in the fixed bed the lowest percentages of retention were in the same order 70 per cent, 24 per cent and 13 per cent.

TABLE IX
COMPARISON OF CREATINE TOLERANCE TESTS (PER CENT RETENTION OF FED CREATINE) IN FIXED BED AND OSCILLATING BED EXPERIMENTS

Periods	Subject E. M.		Subject C. O.		Subject S. W.	
	Fixed Bed	Oscillating Bed	Fixed Bed	Oscillating Bed	Fixed Bed	Oscillating Bed
Control						
last six	88	...	...	...	91	
weeks	...	...	...	...	...	...
	...	...	100	...	98	84
	99	98	91	99	89	
	...	97	...	100	...	100
	...	100	98	100	80	100
Immobilization						
1st week	83	...	...	...	...	82
2nd week	...	87	29	93	46	
3rd week	...	...	56	...	26	64
4th week	76	88	50	81	48	73
5th week	...	81	24	42	44	73
6th week	70	...	...	...	13	
Recovery						
1st week	70	...	27			
2nd week	...	98	...	73	73	84
3rd week	91	100	90	100	...	99
4th week	100	...	95	...	100	
5th week	...	100	...	95	98	89
6th week	...	...	...	...	100	93

8. *17-Ketosteroids:* The excretion of 17-ketosteroids over the entire period of immobilization gave average values which were not significantly lower than those for the control and recovery periods. There was in all three subjects a slight and questionably significant reduction toward the end of the immobilization period. The absence of any correlation between the

changes in nitrogen excretion and 17-ketosteroid excretion is evident in Table x.

In the previous immobilization study only one subject, E. M., had shown a significant decrease in 17-ketosteroid excretion during the period of immobilization in the fixed bed.

TABLE X

URINARY 17-KETOSTEROID EXCRETION (ANALYSES OF SEVEN-DAY POOLED URINE SPECIMENS) AND COMPARISON WITH TOTAL NITROGEN EXCRETION—OSCILLATING BED EXPERIMENT

Periods	Subject E. M.		Subject C. O.		Subject S. W.	
	17-ketosteroids Mg./day	Nitrogen Total Excretion Gm./day	17-ketosteroids Mg./day	Nitrogen Total Excretion Gm./day	17-ketosteroids Mg./day	Nitrogen Total Excretion Gm./day
Control						
1st week	.....	.....	.....	.....	.....	13.43
2nd week	11.05	15.38	12.85	12.86	11.50	13.59
3rd week	8.82	13.61	11.05	11.98	12.10	12.97
4th week	9.30	14.17	9.35	13.15	13.05	12.81
5th week	8.93	13.74	11.80	13.12	11.70	12.85
Average of last 3 control weeks	9.02	13.84	10.73	12.75	12.28	12.88
Immobilization						
1st week	10.50	14.07	11.62	13.00	14.20	12.89
2nd week	9.22	16.10	11.50	13.73	13.50	14.62
3rd week	8.90	15.32	11.10	13.87	10.80	13.77
4th week	8.30	14.34	9.85	13.69	10.01	14.51
5th week	7.90	14.20	9.18	13.20	10.64	13.85
Average of immobilization weeks	8.96	14.81	10.65	13.50	11.83	13.93
Recovery						
1st week	7.12	12.70	10.75	12.98	11.85	13.27
2nd week	10.55	11.83	10.50	12.33	10.70	11.48
3rd week	8.10	11.70	11.60	12.14	9.45	11.66
4th week	9.95	11.92	11.05	11.67	8.85	12.51
5th week	9.25	11.59	12.72	11.56	7.48	12.59
6th week					8.55	12.54
Average of recovery weeks	8.99	11.95	11.32	12.14	9.48	12.34

9. *Other factors in the urine:* Urinary specific gravity measured daily did not change significantly during the various periods of study. On fairly constant fluid intake levels, averaging approximately 2,300 cc. daily, the average daily urine volumes among the three subjects were approximately 250 cc. higher during immobilization than during the control phase. An increase in urine volume of the same extent occurred during the immobilization period in the fixed bed experiment.

10. *Blood chemistry studies:* There were no significant changes in the blood levels of total proteins, phosphorus, sodium and potassium during immobilization in the oscillating bed.

During immobilization in the fixed bed elevations in serum calcium levels were observed in all four subjects. In the present experiment changes in serum calcium were less striking. (Table xi.) In two of the subjects (E. M. and S. W.) the average serum calcium levels during immobilization were slightly higher than the average levels during the control phase.

B. Physiologic Studies. 1. Basal metabolism. Tests of the basal metabolic rate showed a decline among all three subjects during immobilization which ranged from 0.9 to 1.4 calories per square meter per hour. This represents a bare 3.4 per cent average reduction in basal oxygen consumption during immobilization in the oscillating bed. In the fixed bed experiment for these three subjects a 5.1 per cent reduction was found in basal metabolism during immobilization. In the recovery phase following immobilization in the oscillating bed, basal metabolism returned to control levels in two to three weeks.

Determinations on two subjects while the bed was oscillating did not show a significant difference between oxygen consumption during oscillation and in the stationary horizontal position. Oscillation at the speed employed appeared not to increase oxygen consumption in the basal state in the limited number of determinations carried out.

2. *Muscle strength:* Comparison of the decreases in muscle strength during five weeks' immobilization in the fixed and oscillating bed experiments revealed that in the oscillating bed there was a smaller reduction in muscle strength particularly in the immobilized leg muscles.

Strength of the biceps muscle groups showed an average decline among the three subjects of a little less than 5 per cent in each experiment. Strength of the shoulder

and arm muscles tested by the straight arm pull showed an average decline of 8.2 per cent during five weeks in the fixed bed and 3.4 per cent in the oscillating bed. In the leg muscles the strength of the anterior tibial muscle groups declined on an average

3. *Girth of extremities:* Girth of the thighs and calves decreased during the five weeks' immobilization in the oscillating bed to a slightly smaller extent than they had decreased during the same length of time in the fixed bed.

TABLE XI

CHANGES IN SERUM CALCIUM LEVELS DURING IMMOBILIZATION IN OSCILLATING BED

Subject	Control		Five Weeks' Immobilization			Recovery	
	No. of Determinations	Range and Average Value Mg./100 cc.	No. of Determinations	Range and Average Value Mg./100 cc.	Week of Occurrence of Maximal Value	No. of Determinations	Range and Average Value Mg./100 cc.
E. M.	3	11.2 (10.6–11.8)	2	12.4 (12.2–12.6)	3rd	2	11.6 (11.5–11.8)
C. O.	3	12.3 (11.9–13.0)	2	12.2 (11.8–12.7)	5th	2	11.5 (11.5–11.6)
S. W.	3	10.7 (10.5–11.1)	5	11.1 (9.4–12.3)	3rd	2	10.7 (10.3–11.1)

14.3 per cent in the fixed bed and 9.2 per cent in the oscillating bed. The decline in strength of the gastrocnemius-soleus muscle groups in the fixed bed ranged from 13.2 per cent to 26.6 per cent with an average decline of 20.2 per cent; in the oscillating bed the decline in strength ranged from 10.9 per cent to 23.8 per cent with an average decline of 15.6 per cent.

In the recovery phase of the oscillating bed experiment approximately three weeks were required for muscle strength to return to control levels. The time required for recovery of muscle strength was slightly longer (approximately four weeks) following immobilization in the fixed bed.

The re-immobilization of S. W. in a fixed bed for two weeks resulted in a decline of 10 per cent on the average in the strength of the anterior tibial and gastrocnemius-soleus muscle groups. During the first two weeks of immobilization in the first fixed bed experiment the average decline in strength of these muscle groups was 11 per cent, but during the same period of time in the oscillating bed the decline in strength was only 2 per cent.

Analysis of the decreases in the girth of the *thighs* in the two experiments revealed differences which, though not statistically significant, were all in the direction of smaller decreases in girth in the oscillating bed. Analysis of the *calf* measurements of subject S. W., all of which were made with the accurate device previously described,[1] revealed significantly smaller decreases in the oscillating bed experiment. The girth of the calves in S. W. decreased by 4.2 per cent in the oscillating bed and by 5.7 per cent during five weeks in the fixed bed. In subjects E. M. and C. O. measurements made during the fixed bed experiment were not strictly reliable since they were made with a narrow steel tape. However, in each leg of both subjects the decreases in girth of the calves were consistently smaller in the oscillating bed experiment although in subject C. O. the differences were very slight.

Comparison of the girth measurements of S. W. during the two weeks' re-immobilization in the fixed bed with the first two weeks of immobilization in the previous fixed and oscillating bed experiments showed approxi-

mately equal decreases in thigh and calf circumferences in all three experiments.

4. *Tilt table:* Use of the oscillating bed during immobilization tended to prevent deterioration of the mechanisms essential for circulatory control in the erect position, was reached at which circulation became impaired, dizziness and pallor appeared and fainting followed shortly thereafter.

Figure 6 presents a comparison of the results of tilt table tests in the fixed and oscillating bed experiments, showing the

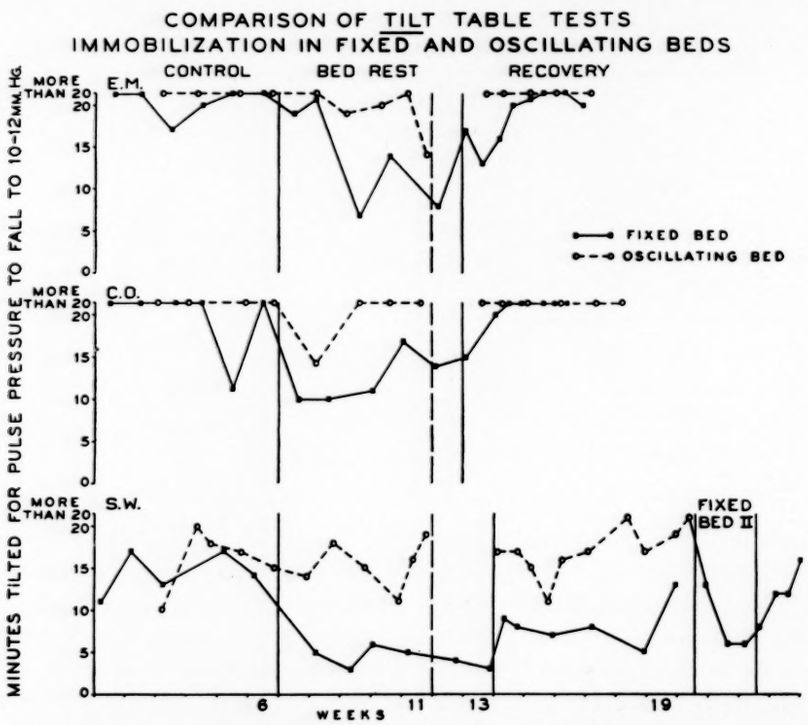


FIG. 6. Comparison of the effect of immobilization in fixed and oscillating beds on the results of tilt table tests, showing the number of minutes in the tilted position (65 degrees feet downward) required for the pulse pressure to fall to critical levels of 10 to 12 mm. of Hg.

which had been found to occur during immobilization of the same subjects in fixed beds. This effect of the oscillating bed was indicated by the uniformly improved reaction of the subjects' circulation and decreased tendency to faint in tilt table tests.

Analysis of tilt table tests performed during the fixed bed experiment and correlation of the data on pulse rate and blood pressure with the observed general reactions of the subjects indicated that the pulse pressure was the most important factor involved in the response of the circulation to tilting. With the subject standing in the upright position on the tilt table it was found that when the pulse pressure fell to between 10 and 12 mm. of mercury, a critical level number of minutes required for the pulse pressure to fall to the critical levels of 10 to 12 mm. when the subjects were tilted to 65 degrees, feet downward. In the fixed bed experiment, during the immobilization phase some impairment of circulatory control began to take place within one week, and the number of minutes required to reach critical pulse pressure levels became markedly reduced within two to three weeks so that actual fainting frequently occurred. In the oscillating bed experiment during the immobilization phase circulatory control was maintained almost at the control level. In the recovery period circulatory control on the tilt table fully returned to the control level within two weeks in this

experiment whereas three to four weeks were required in the fixed bed experiment.

The re-immobilization of S. W. in a fixed bed for two weeks brought about essentially the same degree of circulatory deterioration as had occurred during immobilization in the first fixed bed experiment, only six to eight minutes being required for critical pulse pressure levels to be reached.

Tiny purpuric hemorrhages in the skin of the feet and legs had occurred in all three subjects in tilt table tests during the latter part of the immobilization phase in the fixed bed experiment. However, in the oscillating bed experiment no petechial hemorrhages appeared in any subject.

5. *Blood volume:* The fall in plasma volume and total blood volume during immobilization was almost identical in the fixed and oscillating bed experiments. The decreases in blood volume averaged slightly less during the immobilization in the oscillating bed but not significantly so.

In the fixed bed experiment during immobilization the average decrease in plasma volume in the three subjects was 217 cc. or 6.9 per cent, in total blood volume 295 cc. or 5.7 per cent. In the oscillating bed the average decrease in plasma volume was 190 cc. or 5.9 per cent, in total blood volume 234 cc. or 4.3 per cent.

Re-immobilization of S. W. for two weeks in a fixed bed brought about a 5.0 per cent decrease in plasma volume and 5.2 per cent decrease in total blood volume.

6. *Circulation time:* Decholin and macasol circulation times showed no changes during immobilization in either the fixed or oscillating bed experiments.

7. *Blood coagulation studies:* Studies employed on all three subjects were coagulation time as determined by the Lee-White method and prothrombin time by a modification of the method of Herbert. Coagulation times following the injection of 1 cc. of heparin intravenously both by the Lee-White and capillary tube methods were carried out at approximately two-week intervals on subject S. W., and prothrombin time determinations by the Link-Shapiro method were carried out every other day during the week preceding and the two weeks of re-immobilization of S. W. in a fixed bed. None of these studies indicated a significant influence of bed rest upon blood coagulation.

8. *Exercise tolerance tests:* As in the fixed bed experiment Master tests showed a decrease in exercise tolerance following immobilization. The recovery of exercise tolerance to control levels required three to four weeks following the immobilization in the oscillating bed as against four to six weeks following the immobilization in the fixed bed.

9. *Heart size:* Kymograms of the chest failed to reveal any significant changes in heart size during this experiment. With this technic, as with the standard chest x-ray technic employed in the fixed bed experiment, there was considerable variation in the apparent size of the heart.

10. *Electrocardiograms:* Electrocardiograms taken in the resting horizontal position during control and immobilization periods showed that during immobilization the heart rate was slightly increased and T_2 decreased in height between 1 and 3 mm. These changes were similar to those which occurred during immobilization in the fixed bed.

11. *Resting pulse rate and blood pressure:* During immobilization in the oscillating bed the resting pulse rate increased on an average 3.0 beats per minute (4.3 beats per minute in the fixed bed). During the first three weeks of recovery there was an additional average increase of 3.1 beats per minute, (3.7 beats in the fixed bed). After the third recovery week in both experiments the resting pulse rate declined toward the control level. In the oscillating bed experiment the control level was reached at approximately the fifth recovery week; in the fixed bed experiment the resting pulse rates had not quite reached the control level by the end of the sixth week.

Resting arterial systolic and diastolic

blood pressures did not change significantly in either experiment.

12. *Hematocrits and blood counts:* No significant changes attributable to immobilization occurred in hematocrits, blood cell counts or hemoglobin estimations. There was a gradual fall in hematocrits throughout the experiment ranging from 2.3 to 3.3 volumes per cent, which may be partially accounted for by the withdrawal of blood for chemical studies.

TABLE XII
CHANGES IN BODY WEIGHT DURING THE OSCILLATING BED EXPERIMENT

Subject	Control	Immobilization		Recovery	
	Weight Change (Last Three Weeks) Kg.	No. of Weeks	Weight Change Kg.	No. of Weeks	Weight Change Kg.
E. M.	−0.4	5	−0.7	5	+1.2
C. O.	+0.4	5	+1.1	5	−0.2
S. W.	−0.8	5	−1.2	6	−0.7

13. *Body weight:* As in the fixed bed experiment changes in body weight were small during the various periods of study. (Table XII.)

14. *Various observations of circulation and respiration during oscillation:* An indication of the effect of oscillation upon the venous circulation of the legs and upon the venous return of blood to the heart may be obtained from the continuous direct measurements of venous pressure in the foot veins during oscillation. The average change in venous pressure in subject C. O.'s dorsal foot vein with each change in position of the bed was 136 mm. of water, and in subject S. W.'s dorsal foot vein 148 mm. of water. Observations of foot veins during oscillation revealed that the veins filled in the foot-down position and emptied in the horizontal. Measurements of foot vein to tongue or carotid circulation time were not made.

There was a constant rhythmical variation in the pulse rate of the subjects during oscillation, the pulse rate being slowest in the horizontal position, speeding up gradually as the bed tilted, being the most rapid at the maximum foot-down position then decreasing gradually as the bed rocked back to the horizontal position. The pulse rate was approximately 10 to 12 beats per minute, more rapid in the foot-down position than in the horizontal position.

Tracings of the respiration of the subjects during oscillation made with a pneumograph and with a spirometer showed changes in the average level or position of the diaphragm with each change in position of the bed. As the bed tilted into the foot-down position, the diaphragm and rib cage shifted gradually into a definite inspiratory position; as the bed rocked back to the horizontal position, the diaphragm and rib cage shifted gradually back to the original mid-position. Despite these shifts in the position of the diaphragm, minute ventilation at rest was not greater during oscillation than in the stationary horizontal position.

PSYCHOBIOLOGIC EFFECTS OF IMMOBILIZATION IN AN OSCILLATING BED*

The three subjects of this experiment, none of whom had a major psychiatric disorder, were studied to determine the psychobiologic effects of immobilization in an oscillating bed. Data were collected by psychiatric interviews and recorded on a check list of daily experiences. The list contained sixty-five items relating to physical and mental activity and energy, psychosomatic reactions, mood changes, sleep, sexual behavior and reactions to doctors, nurses and visitors.

The data revealed that the reactions to immobilization were markedly variable from subject to subject, both in pattern and degree, and were expressions of the subject's dominant personality traits.

A subject's immediate reaction to im-

* From the Department of Medicine (Neurology), Cornell University Medical College. This work was carried out by Dr. Keeve Brodman.

mobilization (such as dependency, aggression or suppression of all emotion) was similar to that experienced in other situations of stress and danger, each subject according to his own dominant personality traits. These reactions occurred most markedly during the two days early in the control period when the cast was fitted, again during the first forty-eight hours of immobilization and once more during the first few days after the cast had been removed. In the five weeks of immobilization each subject manifested, either overtly or indirectly, some signs of anxiety, hostility and increased sexual tension. Changes also took place in mental activity, physical activity and the sleep pattern. Complaints of physical discomfort such as impaired sleep and stiffness and soreness of the muscles were minimal and were rarely expressed after the first week. Stiffness of the knees occurred in one subject; this was slight and was present only during the final week in the cast.

Certain physiologic phenomena, such as decrease in appetite, generalized weakness and increased fatigue on exertion were clearly less marked than they had been in a previous immobilization in a fixed bed. In recovery mild dizziness was noted only momentarily, unsteadiness of the legs lasted to the third recovery day, and weakness of the legs for ten days. The subject who reported stiffness of the knees during the final week in the cast continued to have it to a slight degree for three weeks in recovery; this was the same subject who following immobilization in the fixed bed had noted knee stiffness and soreness for several months. The reduction in intensity of these physiologic phenomena is associated with both psychosomatic factors and the effects of oscillation on the circulation.

In all instances these reactions were markedly less than had been noted one year previously when each of the three subjects was immobilized in a fixed bed. Since these reactions are similar to those the subjects experienced in other situations of stress and danger and since in their first experience the subjects had discovered that immobilization was not really to be feared, it would seem that the relative mildness of the reactions in the oscillating bed was related to the fact that this was a second experience with immobilization and not that the bed oscillated. This interpretation is borne out by odservations on a subject (S. W.) who, after having been in a fixed bed and then in an oscillating bed, was immobilized for a third time in a fixed bed. In this third experience, with the exception of muscle stiffness, he had even milder reactions than in the oscillating bed.

COMMENTS

It would appear from these studies that motion of an oscillating bed of the Sanders type modifies favorably or prevents in large measure many of the metabolic and physiologic consequences of immobilization of the healthy adult. In Sanders' description of such a bed in 1936 its use was recommended as an adjuvant in the treatment of congestive heart failure and peripheral vascular disease,[11] and the bed since then has been used principally in the treatment of occlusive arterial disease of the extremities[17–20] and to some extent of phlebothrombosis and thrombophlebitis.[21,22] The present study would suggest that the oscillating bed might also be of benefit in the management of patients who by the nature or severity of their illness are condemned to many weeks of relative immobility.

Influence of Oscillating Bed on Nitrogen Metabolism. Nitrogen losses from immobilization were reduced by approximately 50 per cent in two of the three subjects. There was an associated reduction in the loss of the muscle mass of the legs and in the extent of impairment of muscle strength and creatine metabolism as indicated by the creatine tolerance test. In the third subject (C. O.) the nitrogen loss was rather small in both the fixed and oscillating bed experiments. The oscillating bed was less effective in preventing impairment of muscle mass and strength, the decreases in both being approximately those experi-

enced during his previous immobilization in the fixed bed.

Correlation of Changes in Nitrogen Metabolism with Concomitant Changes in Sulfur, Phosphorus and Potassium. It has been of interest to determine whether the alterations in nitrogen metabolism observed in these studies could be correlated with changes in other protoplasmic constituents, such as sulfur, phosphorus and potassium. It is customary to calculate theoretic nitrogen balances based on the ratio of these elements to nitrogen in muscle protoplasm. Comparison with the measured nitrogen balances would indicate whether or not the reduced nitrogen loss brought about by oscillation represents a saving to the organism of muscle protoplasm. (Tables XIII to XV.)

Sulfur: The generally accepted sulfur: nitrogen ratio in muscle is 1:14. In this study in which only the total urinary sulfur was estimated, the ratio of urinary sulfur: nitrogen was maintained quite constantly throughout the study in the proportion in which these elements are present in muscle protoplasm. This was also the case in the previous study of immobilization in the fixed bed.

Phosphorus: The same calculation was made with respect to phosphorus, assuming a ratio of nitrogen: phosphorus in muscle of 14.7:1[23,24,25] and correcting for phosphorus associated with calcium in the ratio in which these elements are present in bone (1:2.23[24,26]). Although comparison of the theoretic nitrogen balances based on phosphorus excretion revealed a fair agreement from week to week with the measured nitrogen balances, there were significant discrepancies in the total excretion over the five-week period of immobilization. In all three subjects nitrogen excretion during immobilization in the oscillating bed was less by 34 per cent, 12 per cent and 60 per cent, respectively, than was anticipated from the phosphorus excretion. The average ratio of the nitrogen lost to phosphorus lost was 9.4:1 instead of the theoretic 14.7:1. This was in sharp contrast to the findings during five weeks' immobilization in the fixed bed. In only one subject (E. M.) was the nitrogen excretion less (by 29 per cent) than was expected on the basis of phosphorus excretion; in the other three subjects the nitrogen excretion was significantly greater than that calculated from the phosphorus excretion. Thus, during the first five weeks' immobilization in the fixed bed for the same subjects employed in the oscillating bed experiment the average nitrogen: phosphorus loss showed a ratio of 20.3:1. There was no obvious explanation for the discrepancies between these nitrogen: phosphorus ratios and the theoretic ratio of 14.7:1.

These findings suggest the hazards of assuming such a fixed ratio of nitrogen: phosphorus in interpreting metabolic data. It should be pointed out that phosphorus appears to be deposited in protoplasm not only with nitrogen but also with carbohydrate, a circumstance that may in part be responsible for the discrepancies observed. In this connection attention is called to the absence of the expected correlation between the nitrogen and phosphorus changes and the changes in body weight.

Potassium: Analysis of potassium balances in relation to nitrogen excretion is also of interest in this connection because potassium, being the principal intracellular cation, may reflect the extent of protoplasmic catabolism and anabolism. The ratio of nitrogen: potassium in muscle is generally assumed to be 9.5:1 on the basis of surprisingly few chemical analyses in animals and man,[25,28] considering the weight that has been given to this index in metabolic calculation. In both the fixed and oscillating bed experiments potassium tended to move in the same direction as nitrogen. Both elements were lost during the immobilization phase but the quantitative relationships were far from the theoretic. There were wide variations in potassium excretion from week to week, which were particularly marked in the oscillating bed experiment in which there were also pronounced variations from subject to subject. All three subjects sustained

TABLE XIII

METABOLIC BALANCES, SUBJECT E. M., SEVEN-DAY PERIODS

ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium						Sodium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Cont l Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-Line	Intake	Output			Balance	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																														
I	14.44	14.09	1.29	15.38	−0.94	−1.55	0.918	0.088	0.903	0.991	−0.073	−0.128	1.623	1.010	0.680	1.690	−0.067	−0.218	3.76	3.52	0.471	3.99	−0.23	−0.33	4.00	3.90	0.014	3.91	+0.09	−0.14
II	14.45	12.67	0.94	13.61	+0.84	+0.23	0.918	0.079	0.717	0.796	+0.122	+0.067	1.591	0.866	0.526	1.392	+0.199	+0.048	3.76	3.32	0.363	3.68	+0.08	−0.02	4.00	4.00	0.011	4.01	−0.01	−0.24
III	14.45	12.95	1.22	14.17	+0.28	−0.33	0.919	0.107	0.843	0.950	−0.031	−0.086	1.591	0.894	0.629	1.523	+0.068	−0.083	3.76	3.27	0.477	3.75	+0.01	−0.09	4.00	3.65	0.013	3.66	+0.34	+0.11
IV	14.45	12.72	1.02	13.74	+0.71	+0.10	0.919	0.101	0.743	0.844	+0.075	+0.020	1.572	0.818	0.567	1.385	+0.187	+0.036	3.76	3.17	0.384	3.55	+0.21	+0.11	4.00	3.63	0.011	3.64	+0.36	+0.13
Control base-line Average last three weeks	14.45	12.78	1.06	13.84	+0.61	0.0	0.919	0.096	0.768	0.864	+0.055	0.0	1.584	0.859	0.574	1.433	+0.151	0.0	3.76	3.25	0.408	3.66	+0.10	0.0	4.00	3.76	0.012	3.77	+0.23	0.0
Immobilization in oscillating bed																														
V	14.45	12.57	1.50	14.07	+0.38	−0.23	0.919	0.108	0.897	1.005	−0.086	−0.141	1.591	0.986	0.689	1.675	−0.084	−0.235	3.76	3.63	0.453	4.08	−0.32	−0.42	4.00	4.02	0.017	4.04	−0.04	−0.27
VI	14.45	14.81	1.29	16.10	−1.65	−2.26	0.919	0.133	0.733	0.866	+0.053	−0.002	1.591	1.043	0.590	1.633	−0.042	−0.193	3.76	3.60	0.360	3.96	−0.20	−0.30	4.00	3.78	0.013	3.79	+0.21	−0.02
VII	14.45	14.27	1.05	15.32	−0.87	−1.48	0.919	0.126	0.800	0.926	−0.007	−0.062	1.591	0.958	0.626	1.584	+0.007	−0.144	3.76	3.47	0.432	3.90	−0.14	−0.24	4.00	3.60	0.015	3.62	+0.38	+0.15
VIII	14.45	13.34	1.00	14.34	+0.11	−0.50	0.919	0.137	0.743	0.880	+0.039	−0.016	1.591	0.901	0.582	1.483	+0.108	−0.043	3.76	3.29	0.392	3.68	+0.08	−0.02	4.00	4.05	0.012	4.06	−0.06	−0.29
IX	14.45	13.04	1.16	14 20	+0.25	−0.36	0.919	0.149	0.890	1.039	−0.120	−0.175	1.572	0.867	0.624	1.491	+0.081	−0.070	3.76	3.30	0.467	3.77	−0.01	−0.11	4.00	3.86	0.016	3.88	+0.12	−0.11
Average of immobilization	14.45	13.61	1.20	14.81	−0.36	−0.97	0.919	0.130	0.813	0.943	−0.024	−0.079	1.587	0.951	0.622	1.573	+0.014	−0.137	3.76	3.46	0.421	3.88	−0.12	−0.22	4.00	3.86	0.015	3.88	+0.12	−0.11
Recovery																														
X	14.45	11.77	0.93	12.70	+1.75	+1.14	0.918	0.117	0.786	0.903	+0.015	−0.040	1.609	0.830	0.582	1.412	+0.197	+0.046	3.76	3.27	0.326	3.60	+0.16	+0.06	4.00	3.55	0.012	3.56	+0.44	+0.21
XI	14.45	10.70	1.13	11.83	+2.62	+2.01	0.919	0.094	0.924	1.018	−0.099	−0.154	1.572	0.723	0.696	1.419	+0.153	+0.002	3.76	3.17	0.409	3.58	+0.18	+0.08	4.00	4.04	0.016	4.06	−0.06	−0.29
XII	14.45	10.79	0.91	11 70	+2.75	+2.14	0.918	0.085	0.740	0.825	+0.093	+0.038	1.591	0.780	0.574	1.354	+0.237	+0.086	3.76	3.15	0.350	3.50	+0.26	+0.16	4.00	3.84	0.012	3.85	+0.15	−0.08
XIII	14.45	10.92	1.00	11.92	+2.53	+1.92	0.919	0.094	0.707	0.801	+0.118	+0.063	1.591	0.734	0.552	1.286	+0.305	+0.154	3.76	3.42	0.323	3.74	+0.02	−0.08	4.00	3 70	0.014	3.71	+0.29	+0.06
XIV	14.45	10.06	1.53	11.59	+2.86	+2.25	0.918	0.077	0.843	0.920	−0.002	−0.057	1.591	0.736	0.647	1.383	+0.208	+0.057	3.76	3.41	0.514	3.95	−0.19	−0.29	4.00	3.88	0.030	3.91	+0.09	−0.14

TABLE XIV

METABOLIC BALANCES, SUBJECT C. O., SEVEN-DAY PERIODS

ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium						Sodium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																														
I	14.44	11.30	1.56	12.86	+1.58	−0.08	0.918	0.176	0.690	0.866	+0.052	+0.042	1.623	0.950	0.457	1.407	+0.216	+0.025	3.76	3.52	0.227	3.75	+0.01	−0.06	4.00	3.65	0.013	3.66	+0.34	−0.13
II	14.32	10.48	1.50	11.98	+2.34	+0.68	0.899	0.218	0.719	0.937	−0.038	−0.048	1.590	0.868	0.463	1.331	+0.259	+0.068	3.76	3.39	0.273	3.66	+0.10	+0.03	4.00	3.39	0.015	3.41	+0.59	+0.12
III	14.45	11.93	1.22	13.15	+1.30	−0.36	0.919	0.239	0.612	0.851	+0.068	+0.058	1.591	1.000	0.399	1.399	+0.192	+0.001	3.76	3.68	0.189	3.87	−0.11	−0.18	4.00	3.83	0.011	3.84	+0.16	−0.31
IV	14.45	11.73	1.39	13.12	+1.33	−0.33	0.919	0.212	0.706	0.918	+0.001	−0.009	1.572	0.991	0.459	1.450	+0.122	−0.069	3.76	3.32	0.212	3.53	+0.23	+0.16	4.00	3.32	0.014	3.33	+0.67	+0.20
Control base-line																														
Average last three weeks	14.41	11.38	1.37	12.75	+1.66	0.0	0.912	0.223	0.679	0.902	+0.010	0.0	1.584	0.953	0.440	1.393	+0.191	0.0	3.76	3.46	0.225	3.69	+0.07	0.0	4.00	3.52	0.013	3.53	+0.47	0.0
Immobilization in oscillating bed																														
V	14.45	11.64	1.36	13.00	+1.45	−0.21	0.919	0.243	0.776	1.019	−0.100	−0.110	1.591	1.006	0.536	1.542	+0.049	−0.142	3.76	3.55	0.262	3.81	−0.05	−0.12	4.00	3.76	0.020	3.78	+0.22	−0.25
VI	14.45	12.69	1.04	13.73	+0.72	−0.94	0.919	0.282	0.594	0.876	+0.043	+0.033	1.591	1.056	0.432	1.488	+0.103	−0.089	3.76	3.55	0.176	3.73	+0.03	−0.04	4.00	3.71	0.020	3.73	+0.27	−0.20
VII	14.45	12.85	1.02	13.87	+0.58	−1.08	0.919	0.306	0.610	0.916	+0 003	−0.007	1.591	1.006	0.420	1.426	+0.165	−0.026	3.76	3.23	0.180	3.41	+0.35	+0.28	4.00	3.52	0.014	3.53	+0.47	0 0
VIII	14.45	12.34	1.35	13.69	+0.76	−0.90	0.919	0.304	0.706	1.010	−0.091	−0.101	1.591	1.038	0.465	1.503	+0.088	−0.103	3.76	2.97	0.218	3.19	+0.57	+0.50	4.00	3.78	0.016	3.80	+0.20	−0.27
IX	14.45	11.70	1.50	13.20	+1.25	−0.41	0.919	0.287	0.779	1.066	−0.147	−0.157	1.572	0.997	0.452	1.449	+0.123	−0.068	3.76	3.16	0.259	3.42	+0.34	+0.27	4.00	3.74	0.015	3.76	+0.24	−0.23
Average of immobilization	14.45	12.25	1.25	13.50	+0.95	−0.71	0.919	0.284	0.693	0.977	−0.058	−0.068	1.587	1.021	0.461	1.482	+0.105	−0.086	3.76	3.29	0.219	3.51	+0.25	+0.18	4.00	3.70	0.017	3.72	+0.28	−0.19
Recovery																														
X	14.45	11.35	1.63	12.98	+1.47	−0.19	0.918	0.220	0.829	1.049	−0.131	−0.141	1.609	0.941	0.540	1.481	+0.128	−0.063	3.76	3.29	0.273	3.56	+0.20	+0.13	4.00	3.40	0.014	3.41	+0.59	+0.12
XI	14.45	10.60	1.73	12.33	+2.12	+0.46	0.919	0.177	0.700	0.877	+0.042	+0.032	1.572	0.971	0.457	1.428	+0.144	−0.047	3.76	3.24	0.283	3.52	+0.24	+0.17	4.00	3.60	0.026	3.63	+0.37	−0.10
XII	14.45	10.37	1.77	12.14	+2.31	+0.65	0.919	0.152	0.696	0.848	+0.070	+0.060	1.591	0.935	0.474	1.409	+0.182	−0.009	3.76	3.00	0.297	3.30	+0.46	+0.39	4.00	3.50	0.015	3.52	+0.48	+0.01
XIII	14.45	10.03	1.64	11.67	+2.78	+1.12	0.919	0.131	0.612	0.743	+0.176	+0.166	1.591	0.870	0.417	1.287	+0.304	+0.113	3.76	3.32	0.286	3.61	+0.15	+0.08	4.00	3.55	0.017	3.57	+0.43	−0.04
XIV	14.45	9.91	1.65	11.56	+2.89	+1.23	0.918	0.119	0.610	0.729	+0.189	+0.179	1.591	0.859	0.420	1.279	+0.312	+0.121	3.76	3.66	0.326	3.99	−0.23	−0.30	4.00	3.59	0.018	3.61	+0.39	−0.08

TABLE XV

METABOLIC BALANCES, SUBJECT S. W., SEVEN-DAY PERIODS

ALL DATA GIVEN AS AVERAGE GM. PER DAY FOR THE PERIOD

Period No.	Nitrogen						Calcium						Phosphorus						Potassium						Sodium					
	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line	Intake	Output			Balance	Variation from Control Base-line
		Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total				Urine	Feces	Total		
Control																														
I*	14.43	12.49	0.94	13.43	+1.00	−0.55	0.919	0.250	0.380	0.630	+0.289	+0.188	1.628	1.040	0.312	1.352	+0.276	+0.087	3.76	3.10	0.284	3.38	+0.38	0.0	4.00	3.05	0.011	3.06	+0.94	+0.42
II	14.43	11.94	1.65	13.59	+0.84	−0.71	0.920	0.285	0.652	0.937	−0.017	−0.118	1.623	1.039	0.575	1.614	+0.009	−0.180	3.76	2.66	0.583	3.24	+0.52	+0.14	4.00	4.62	0.024	4.64	−0.64	−1.16
III	14.43	11.86	1.11	12.97	+1.46	−0.09	0.920	0.261	0.533	0.794	+0.126	+0.025	1.626	0.954	0.452	1.406	+0.220	+0.031	3.76	3.15	0.453	3.60	+0.16	−0.22	4.00	2.98	0.014	2.99	+1.01	+0.49
IV	14.43	11.29	1.52	12.81	+1.62	+0.07	0.920	0.261	0.672	0.933	−0.013	−0.114	1.623	0.919	0.593	1.512	+0.111	−0.078	3.76	2.79	0.654	3.44	+0.32	−0.06	4.00	3.93	0.041	3.97	+0.03	−0.49
V	14.42	11.66	1.19	12.85	+1.57	+0.02	0.921	0.235	0.496	0.731	+0.190	+0.089	1.604	0.951	0.417	1.368	+0.236	+0.047	3.76	2.70	0.404	3.10	+0.66	+0.28	4.00	3.45	0.029	3.48	+0.52	0.0
Control base-line																														
Average last three weeks	14.43	11.61	1.27	12.88	+1.55	0.0	0.920	0.252	0.567	0.819	+0.101	0.0	1.618	0.942	0.487	1.429	+0.189	0.0	3.76	2.88	0.504	3.38	+0.38	0.0	4.00	3.45	0.028	3.48	+0.52	0.0
Immobilization in oscillating bed																														
VI	14.43	11.56	1.33	12.89	+1.54	−0.01	0.920	0.279	0.647	0.926	−0.006	−0.107	1.607	1.064	0.540	1.604	+0.003	−0.186	3.76	3.21	0.509	3.72	+0.04	−0.34	4.00	3.92	0.015	3.94	+0.06	−0.46
VII	14.48	13.36	1.26	14.62	−0.14	−1.69	0.921	0.355	0.576	0.931	−0.010	−0.111	1.646	1.196	0.517	1.713	−0.067	−0.256	3.76	3.40	0.447	3.85	−0.09	−0.47	4.00	4.01	0.019	4.03	−0.03	−0.55
VIII†	14.70	12.55	1.22	13.77	+0.93	−0.62	0.930	0.403	0.647	1.050	−0.120	−0.221	1.641	1.177	0.507	1.684	−0.043	−0.232	3.76	3.09	0.397	3.49	+0.27	−0.11	4.00	3.31	0.014	3.32	+0.68	+0.16
IX	14.73	13.15	1.36	14.51	+0.22	−1.33	0.930	0.428	0.679	1.107	−0.177	−0.278	1.660	1.217	0.542	1.759	−0.099	−0.288	3.76	2.71	0.417	3.13	+0.63	+0.25	4.00	3.66	0.026	3.69	+0.31	−0.21
X	14.70	12.51	1.34	13.85	+0.85	−0.70	0.931	0.445	0.660	1.105	−0.174	−0.275	1.638	1.154	0.509	1.663	−0.025	−0.214	3.76	2.60	0.379	2.98	+0.78	+0.40	4.00	3.66	0.022	3.68	+0.32	−0.20
Average of Immobilization	14.61	12.63	1.30	13.93	+0.68	−0.87	0.926	0.382	0.642	1.024	−0.098	−0.199	1.639	1.162	0.523	1.685	−0.046	−0.235	3.76	3.00	0.430	3.43	+0.33	−0.05	4.00	3.71	0.019	3.73	+0.27	−0.25
Recovery																														
XI	14.75	11.93	1.34	13.27	+1.48	−0.07	0.930	0.326	0.689	1.015	−0.085	−0.186	1.682	1.031	0.512	1.543	+0.139	−0.050	3.76	2.44	0.489	2.93	+0.83	+0.45	4.00	3.27	0.042	3.31	+0.69	+0.17
XII	14.70	10.12	1.36	11.48	+3.22	+1.67	0.931	0.223	0.619	0.842	+0.089	−0.012	1.638	0.947	0.480	1.427	+0.211	+0.022	3.76	2.69	0.417	3.11	+0.65	+0.27	4.00	3.20	0.025	3.23	+0.77	+0.25
XIII	14.70	10.37	1.29	11.66	+3.04	+1.49	0.930	0.185	0.589	0.774	+0.156	+0.055	1.641	0.919	0.467	1.386	+0.255	+0.066	3.76	2.69	0.434	3.12	+0.64	+0.26	4.00	3.75	0.034	3.78	+0.22	−0.30
XIV	14.75	11.29	1.22	12.51	+2.24	+0.69	0.931	0.167	0.552	0.719	+0.212	+0.111	1.679	1.004	0.494	1.498	+0.181	−0.008	3.76	2.85	0.470	3.32	+0.44	+0.06	4.00	4.03	0.035	4.07	−0.07	−0.59
XV	14.70	11.36	1.23	12.59	+2.11	+0.56	0.930	0.147	0.579	0.726	+0.204	+0.103	1.641	0.963	0.529	1.492	+0.149	−0.040	3.76	2.87	0.434	3.30	+0.46	+0.08	4.00	4.10	0.025	4.13	−0.13	−0.65
XVI	14.72	11.30	1.24	12.54	+2.18	+0.63	0.931	0.159	0.534	0.693	+0.238	+0.137	1.660	0.959	0.483	1.442	+0.218	+0.029	3.76	2.84	0.492	3.33	+0.43	+0.05	4.00	3.62	0.061	3.68	+0.32	−0.20
XVII‡	14.70	11.45	1.26	12.71	+1.99	+0.44	0.931	0.185	0.465	0.650	+0.281	+0.180	1.649	0.967	0.447	1.414	+0.235	+0.046	3.76	2.81	0.447	3.26	+0.50	+0.12	4.00	4.37	0.056	4.43	−0.43	−0.95
New control																														
Base-line for fixed bed II§	14.71	11.36	1.24	12.60	+2.11	0.0	0.931	0.160	0.536	0.696	+0.235	0.0	1.650	0.962	0.493	1.455	+0.195	0.0	3.76	2.84	0.460	3.30	+0.46	0.0	4.00	3.97	0.046	4.02	−0.02	0.0
Immobilization, fixed bed II																														
XVIII	14.75	11.88	1.45	13.33	+1.42	−0.69	0.931	0.240	0.554	0.794	+0.137	−0.098	1.679	1.036	0.507	1.543	+0.136	−0.059	3.76	3.40	0.457	3.86	−0.10	−0.56	4.00	4.12	0.020	4.14	−0.14	−0.12
XIX	14.70	13.41	1.45	14.86	−0.16	−2.27	0.930	0.383	0.612	0.995	−0.065	−0.300	1.627	1.191	0.529	1.720	−0.093	−0.288	3.76	2.83	0.434	3.26	+0.50	+0.04	4.00	3.54	0.019	3.56	+0.44	+0.46
Recovery																														
XX	14.75	11.37	1.53	12.90	+1.85	−0.26	0.931	0.312	0.572	0.884	+0.047	−0.188	1.679	1.052	0.520	1.572	+0.107	−0.088	3.76	2.66	0.446	3.11	+0.65	+0.19	4.00	3.54	0.054	3.59	+0.41	+0.43

* 5-day period.

† The slight increase in nitrogen, calcium and phosphorus intake beginning at period VIII occurred because of the necessity for using "emergency" bread made from dark flour.

‡ 4-day period.

§ Average of periods XV, XVI and XVII.

potassium losses during the first two weeks of immobilization in the oscillating bed at a time when the nitrogen losses were also maximal. Thereafter, despite continued nitrogen losses S. W. and C. O. actually stored potassium; the magnitude of the storage of the potassium by C. O. was such that his overall potassium balance for the entire immobilization period was slightly positive. E. M., on the other hand, lost potassium throughout the immobilization period although there was a decline in his potassium excretion toward equilibrium during the last two weeks.

These variations from subject to subject in potassium excretion during the oscillating bed experiment are pointed up by comparison of the theoretic nitrogen losses based on potassium, employing the ratio given above, with the measured nitrogen losses. In E. M., for example, the theoretic nitrogen loss based on potassium excretion exceeded the actual loss by 115 per cent. In S. W. it was less than the actual nitrogen loss by 46 per cent, in C. O. by 342 per cent. On the other hand, during immobilization in the fixed bed the theoretic nitrogen losses based on potassium excretion exceeded the measured nitrogen losses in all three subjects.

There is no ready explanation for these observed discrepancies between potassium and nitrogen excretion. A potential source of variation in potassium excretion may arise from shifts in body glycogen and intracellular fluid.[27] A more likely source for these discrepancies would appear to be irregular variations in the potassium content of the diets. In this study this variable was checked by direct analysis of the dietary intake. Nine analyses of the 2,800 calorie diet carried out during different seasons over the two-year period showed a standard deviation of the potassium values of ± 0.18 Gm. (4.8 per cent).[13] Although these analyses showed little variation, it is possible that more frequent analyses might have revealed greater variations in diet potassium content. This is suggested by the appearance of occasional simultaneous trends in potassium excretion in the different subjects which were independent of the stage of the experiment. The unreliability of the nitrogen:potassium ratio as a quantitative index of protoplasmic shifts has also been pointed out by other investigators.[29]

Influence of Oscillating Bed on Calcium Metabolism. Oscillation exerted a striking effect upon the changes in calcium metabolism resulting from immobilization, an effect of considerable interest because of its relation to the problem of urinary tract stone formation in immobilized patients. It had been found in the study of four normal subjects immobilized in fixed beds that the average total urinary calcium excretion was approximately one-half to two-thirds that shown by a group of young men immobilized for four or five weeks because of fracture or osteotomy,[30] and the levels of urinary calcium in two of the subjects were well within the range of the fracture group. It had also been shown that during immobilization in the fixed bed certain factors concerned with the solubility of calcium in the urine failed to make appropriate compensatory responses to the increased excretion of calcium. Urinary volume increased very slightly, urinary pH became slightly more alkaline and urinary citric acid, the influence of which in favoring calcium solubility resides in the formation of a weakly ionized and very soluble calcium citrate complex, remained relatively unchanged. This was in contrast to what occurs in the normal ambulatory individual in whom a shift in urine toward the alkaline side and an increase in urinary calcium excretion is regularly accompanied by an increase in urinary citric acid.[31] The absence of these compensatory responses, the associated increase in urinary phosphorus and the significant increases in urinary calcium during immobilization would all favor the precipitation of calcium phosphatic calculi in the urinary tract. These findings are of considerable interest in view of the rather high incidence of stone formation observed in immobilized patients in service hospitals during the

recent war[32,33,34] and previously reported by others.[35,36]

The total loss of urinary calcium during immobilization in the oscillating bed was approximately one-half of that shown by the same subjects immobilized in the fixed bed experiment. The inference that this decrease in calcium loss during immobilization was due to oscillation and not to other factors appeared to be substantiated by the magnitude of the calcium loss which occurred when one of the subjects was immobilized in a fixed bed for a second time. During this re-immobilization of S. W. in a fixed bed for two weeks calcium was lost at the same rapid rate as during his first immobilization in a fixed bed one year previously. Oscillation had no effect upon urinary pH, urinary volume and urinary citric acid. However, in view of the influence of oscillation in reducing the extent of the urinary calcium and phosphorus losses during immobilization this procedure should reduce the hazard of stone formation in the urinary tract during immobilization.

Influence of Oscillation on Circulation. The oscillating bed tended to prevent the deterioration of the mechanisms responsible for circulatory control in the upright position as tested by means of a tilt table. During immobilization in the fixed bed, tilt table tests had demonstrated progressive impairment of circulatory control in the upright position, with an increased tendency to faint, which became pronounced within two to three weeks. In contrast, similar tests carried out during the oscillating bed experiment revealed that control of the circulation in the upright position was maintained almost at control levels throughout the immobilization phase.

Observations during the fixed bed experiment had indicated that the legs were the principal vascular area in which important derangements occurred in the response of the blood vessels to the upright position. Binding the legs to the groin with Ace bandages prevented fainting when the subject stood in the erect position on the tilt table whereas binding of the abdomen was ineffective. Measurements of the circumference of the legs during tilt table tests had shown greater increases in the size of the legs in the tilted position during the immobilization phase than during the control period. Analysis of the changes in the leg circumference during and after tilting suggested that during immobilization there was impairment of either venous or muscular tone or both. Repetition of these leg measurements during tilt table tests in the oscillating bed experiment revealed that during immobilization, although the subjects stood in the upright position for longer periods of time (as compared with the fixed bed experiment), the increases in the circumference of the legs were not as great. This would suggest that by some mechanism, oscillation tended to prevent impairment of venous or muscular tone in the legs. The occurrence of purpuric hemorrhages in the skin of the legs in tilt table tests during immobilization in the fixed bed and the absence of petechiae in tests during the comparable stage in the oscillating bed experiment would indicate that appreciable capillary wall fragility was prevented by oscillation.

The beneficial effects frequently observed following the use of the oscillating bed in vascular diseases of the lower extremities have been attributed to improvement in blood flow brought about by the motion of the bed. No conclusive evidence for this action has been presented although some attempts have been made to measure peripheral circulation under these conditions. Horton, Krusen and Sheard[20] measured skin temperatures during oscillation with equivocal results. The studies of Barker and Roth[37] indicated that oscillation raised the skin temperature of the extremities, but their observations were not carried out under carefully controlled environmental conditions. Although the present study did not include direct measurements of blood flow, rhythmic fluctuations in venous pressure as measured in the dorsal vein of the foot were of interest. The venous pressure changed 140 mm. of water with each oscillation of

the bed. The veins could be seen alternately to fill and empty with each oscillation. This may mean that in the presence of competent venous valves a larger volume of venous blood is delivered to the right auricle during oscillation.

Influence of Oscillation on Respiratory Function. Measurements of respiratory function showed a shift in the average level of the diaphragm with each change in position of the bed. This might be regarded as a favorable effect since it would lead to the aeration at intervals of portions of the lungs which would not be aerated at the constant diaphragm level prevailing at rest in a fixed bed. However, the actual volume of pulmonary ventilation per unit of time was not increased by oscillation. The changes in the position of the diaphragm take place gradually over a period of time equal to the cycle of the bed (one and three-quarter minutes in this experiment).

Of some interest in relation to the possible use of the oscillating bed with cardiac patients was the finding that oscillation at the speed employed did not increase the metabolic rate over that in the resting horizontal position. Subsequent studies on other patients have confirmed this finding.

Blood Coagulation Mechanism. It is worthy of emphasis that no increased tendency for the blood to coagulate during immobilization was found in either the fixed or oscillating bed experiments. In particular, prior to and during the re-immobilization of subject S. W. in a fixed bed an increased number and variety of tests were employed (heparin tolerance test weekly, prothrombin time determinations every other day, and Lee-White and capillary tube coagulation times every other day) without the detection of significant alterations in the blood coagulation mechanism.

Effect of Oscillation on Recovery from Immobilization. The restoration of metabolic and physiologic indices to normal came about more rapidly following immobilization in the oscillating than in the fixed bed. Physiologic function returned to normal more promptly than did the metabolic. Indeed, the delay in the return to normal of metabolic function in both experiments should be emphasized. In neither experiment had the nitrogen and calcium metabolism fully reverted to control levels during the recovery periods of four to six weeks. There was also considerable individual variability in the speed of recovery. The somewhat more rapid improvement in nitrogen and calcium balances during recovery in the oscillating bed experiment was attributable to at least three factors: (1) The balances were less negative during immobilization in the oscillating bed and hence a smaller shift was required to reach a positive balance. (2) The immobilization phase in the oscillating bed experiment was one to two weeks shorter; hence the aggregate of the catabolic changes was considerably less than in the fixed bed experiment. (3) The subjects were psychologically ready for and initiated mobile activity three days earlier in the oscillating bed recovery period. These modifying factors may in part account for the fact that most physiologic functions (basal metabolic rate, muscle strength, girth of extremities, the reaction of the circulation to the erect position, exercise tolerance and the reclining pulse rate) returned to control levels from one to two weeks earlier in the recovery phase following immobilization in the oscillating than in the fixed bed.

Repetition of Fixed Bed Experiment. At the conclusion of the oscillating bed experiment subject S. W. was immobilized in a fixed bed for a second time in order to provide a check on the results of the previous fixed bed experiment. This procedure would also test the validity of the conclusion that the differences in the results of the fixed and oscillating bed experiments were specifically due to oscillation and not to any interval change in the condition of the patient. During this two weeks of re-immobilization in a fixed bed the metabolic and physiologic derangements which occurred duplicated very closely in pattern and extent the changes which had occurred during the first two weeks of this subject's first im-

mobilization in a fixed bed a year previously. In most respects the changes were significantly greater than had occurred during the first two weeks of his antecedent immobilization in an oscillating bed. The differences in the results of the fixed bed and oscillating bed experiments are therefore attributable to the modifying effects of oscillation rather than to changes in the subject's growth, development or physical condition.

Mechanism of Action of Oscillating Bed. The mechanism by which the oscillating bed serves to ameliorate the effects of immobilization is not clear. It is believed that the principal factors may be an increased circulation through the extremities and partial weight-bearing in the foot-downward position. The rocking motion of the bed which places the legs alternately in a dependent position and in a slightly elevated position is identical in principle to Buerger's postural exercises, long in use in the treatment of conditions resulting from defective peripheral circulation. The oscillating bed is superior to Buerger's exercises, however, in that the changes in posture can be repeated continuously for many hours without physical effort on the part of the subject or patient. In regard to weight-bearing it is evident from actually experiencing the motion of the bed that if a foot-board is used or the legs and feet enclosed in a cast, partial weight-bearing definitely occurs provided the bed is tilted to a sufficient angle. This action probably transmits some stress or strain to the body, particularly to the skeleton, and also brings about slight muscular contraction, principally in the gastrocnemius-soleus and quadriceps muscle groups. Muscular contraction *may* in turn call for greater blood flow. It is conceivable that skeletal stress and the stimulation to slight muscular contraction may act to discourage catabolic and encourage anabolic processes.

It is to be noted that in this experiment oscillation was begun at the start of the immobilization period. Whether or not oscillation would reduce metabolic losses once they become well established cannot be determined from this experiment.

It is uncertain what the optimal daily period for oscillation should be. In one of the subjects the oscillating bed was in motion twenty-one hours a day; in the other two subjects, E. M. and C. O. who were studied together, the bed was in motion eight hours daily because of the fact that two oscillating beds were not exclusively available during the period of the experiment. There was no evidence that the longer period of oscillation was more effective.

CONCLUSIONS

It seems reasonable to conclude from these findings that the oscillating bed may in considerable measure prevent many of the deleterious effects consequent upon prolonged immobilization. These beneficial effects are exerted on the mechanism responsible for circulatory control in the erect position, on the changes in muscle mass and strength and on creatine, nitrogen, calcium and phosphorus metabolism. The metabolic effects exerted by oscillation would serve to reduce the likelihood of calculus formation in the urinary tract. The oscillating bed is a simple and practical device, readily available, generally comfortable and capable of saving considerable nursing and physiotherapeutic care. On the basis of these findings it seems reasonable to suggest that the oscillating bed may provide a valuable adjunct in the management of patients immobilized for long periods because of fractures, severe burns, spinal cord injuries or paralysis resulting from poliomyelitis. This suggestion is made with the reservation that the beneficial effects of oscillation on physiologic and metabolic functions in immobilized healthy adults may not necessarily occur in diseased states. This uncertainty can be resolved only by direct experimental trial.

SUMMARY

A study was made of the influence of an oscillating bed on the metabolic and

physiologic disturbances associated with immobilization. The subjects were three normal healthy young men. The investigation was carried out on a metabolism ward during control (four to five weeks), immobilization (five weeks) and recovery (five to six weeks) periods. The dietary intake was constant. During the immobilization periods the subjects were in bivalved plaster casts extending from umbilicus to toes. One year previously the three subjects studied had participated in an experiment identical with the present study except that they had been immobilized in standard (fixed) hospital beds. During immobilization in the oscillating bed:

1. Nitrogen excretion increased in the same general pattern as in the fixed bed experiment; but in two of the subjects nitrogen loss was approximately half as great as during an equal period of immobilization in the fixed bed.

2. The loss of calcium, chiefly in the urine, was, on the average, half as great as during the same period in the fixed bed.

3. The loss of phosphorus was significantly less in two of the subjects than during the same period in the fixed bed.

4. Although urinary citric acid, pH and urine volume did not appreciably change, the significant reduction in urinary calcium and phosphorus losses would render the precipitation of calcium phosphate in the urinary tract less likely than during immobilization in a fixed bed.

5. There was good correlation between the excretion of urinary total sulfur and nitrogen on the basis of the ratio in which they exist in muscle. The correlation between nitrogen and phosphorus on the same basis was less good, between nitrogen and potassium poor.

6. Creatine tolerance tests indicated that creatine metabolism was significantly less impaired than during immobilization in the fixed bed. The decrease in muscle mass and strength of the immobilized limbs was also less than during an equal period in the fixed bed.

7. Changes in basal oxygen consumption were not significant.

8. The deterioration produced by fixed bed immobilization in the mechanisms essential for adequate circulation in the erect position (as measured by tilt table tests) was largely prevented.

9. Measurements of venous pressure in the foot veins during oscillation revealed an average change in pressure of 140 mm. of water with each change in position of the bed. A rhythmical shift was observed in the average level of the diaphragm with each change in position of the bed, without significant alteration in the pulmonary minute ventilation.

10. Changes in urinary 17-ketosteroid excretion and in serum calcium levels were not significant.

11. As in the fixed bed experiment, there were no significant alterations in blood coagulation studies, circulation time, heart size or electrocardiograms.

During the recovery phase most metabolic and physiologic functions returned to control levels or became re-stabilized more rapidly than following immobilization in the fixed bed.

Following recovery from the oscillating bed experiment, one subject was re-immobilized in a fixed bed for two weeks. The results duplicated closely the changes observed during the first two weeks of his first immobilization in a fixed bed a year previously.

The authors wish to express their deep appreciation to Miss Hertha H. Taussky of this department for her direction of the citric acid studies in this and the previous report.

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Effect of Vomiting Due to Intestinal Obstruction on the Serum Potassium*

Chemical and Electrocardiographic Observations in Fifteen Cases Preliminary Report

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UNTIL recently alkalosis accompanying vomiting was commonly regarded as being associated with the balance of sodium and chloride in extracellular fluids and little significance was attached to incidental changes in other electrolytes and in the ionic constitution of the cells themselves. Recently the reports of Butler,[1] Fenn,[2] Darrow,[3,4] Talbott,[5] Gamble[6] and others have called attention to the alterations in the intracellular as well as extracellular fluid which occur during alkalosis and the acidosis which accompanied loss of fluids from the body. Specifically, it has been shown that sodium may pass from the extracellular fluid into the cells and replace potassium. Darrow[3] has shown that there is a marked loss of potassium accompanying states associated with dehydration, particularly diarrhea in infants. Similar losses of potassium have also been shown to occur in other conditions to be discussed later.

In 1938 Scudder and associates[7] studied a series of twenty untreated patients with intestinal obstruction and found the serum potassium to be raised in seven, low in five and normal in eight. They also found that the cellular potassium in these untreated patients was low in fourteen of the twenty. Falconer[8a,b] (1939) was unable to verify that either hypopotassemia or hypercalcemia were factors in intoxication accompanying intestinal obstruction. He found that there was a tendency for the concentration of potassium, sodium and calcium in the serum to decrease, the reduction in potassium tending to be relatively the largest.

In view of these observations, and more particularly because we were struck by the similarity of the electrocardiographic changes associated with intestinal obstruction to those of hypopotassemia in other conditions, we decided to study the electrocardiographic findings in intestinal obstruction accompanied by vomiting, to compare the electrocardiographic changes with the levels of serum potassium and to determine the effect of administration of potassium upon these changes. We wish to report our observations on the electrolyte changes, particularly as they concern the serum potassium, in fifteen cases of acute intestinal obstruction. Since we wish to emphasize the value of the electrocardiograph, not only in detecting the presence of hypopotassemia in intestinal obstruction but also in following, in a rough way, the fluctuations of the serum concentration of this electrolyte, the electrocardiographic findings in hypopotassemia will be briefly discussed before the details of our observations are presented.

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ELECTROCARDIOGRAPHIC CHANGES ASSOCIATED WITH LOW SERUM POTASSIUM

The electrocardiographic findings in hyperpotassemia are quite well established.[9a–e] The characteristic tall, narrow T waves, often accompanied by some widening of the QRS complexes, are reversible and give way to normal waves as the hyperpotassemia becomes lowered toward normal. The electrocardiographic alterations associated with a low serum potassium have received less study. In 1937 Bellet and Dyer[10] reported characteristic electrocardiographic changes in twenty-three patients after their emergence from diabetic acidosis. These changes consisted of a lengthening of the Q-T interval, depression of the S-T segment and, in some instances, inversion of the T waves. The relation of these changes to hypopotassemia was not established at that time. However, the relationship of characteristic electrocardiographic changes in hypopotassemia and in diabetic acidosis has been well established by the more recent studies of Holler,[12] Nicholson and Branning, Martin and Wertman[13] and Nadler, Bellet and Lanning.[14]

MATERIAL AND METHOD OF STUDY

The ages of our patients ranged from twenty-five to eighty-seven years; four patients were seventy years of age or older, five were between sixty and seventy, three were between fifty and sixty and three were between twenty-five and fifty years of age. The series consisted of nine men and six women. Thirteen patients were white and two were negroes. The diagnoses were: Duodenal ulcer with pyloric obstruction in four patients; carcinoma of the large bowel with intestinal obstruction in three patients; obstructing carcinoma of the stomach in two patients; strangulated hernia in one patient and cholelithiasis with peritonitis and intestinal obstruction in one patient.

TABLE I

SERUM CONCENTRATIONS, CASE 9

C. J., aged seventy; diagnosis: carcinoma of colon.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Chloride (mEq./L.)	CO_2 (mEq./L.)	Urea (mg. %)	Remarks
1/6/48	3.6	140	4.4				
1/7/48	2.8	149	4.9				
1/8/48	3.3	137	4.9	85	27		
1/9/48	2.5	138	4.3				
1/10/48							
2:30 P.M.	2.9	139	4.7	..	..	..	Before KCl
4 P.M.	4.5	140	4.3	94.2	..	..	After 500 ml. KCl I.V.
11 P.M.	3.8	132	...	..	..	..	6½ hr. after KCl
1/12/48	3.8	117	4.9	..	45	100	
1/14/48	2.7	129	4.5	74	17		
1/15/48	2.9	132	...	69	21	70	
1/21/48	3.8	137	4.1	86	..	30	
2/5/48	5.4	140	5.3				

As one would anticipate most of these patients were quite ill on admission. They manifested varying degrees of dehydration through loss of fluid by vomiting and in addition, in a few patients, by diarrhea. Mental symptoms ranging from disorientation to coma were observed in some and many presented the picture of shock.

As soon as possible after admission and diagnosis blood was drawn and estimations made of the serum potassium, sodium and calcium, the CO_2 combining power and plasma chloride. These studies were instituted before therapy in five patients (Cases 9, 10, 13, 14 and 15) and after treatment had been started in the ten remaining patients. These chemical studies were repeated at frequent intervals during the continuance of therapy until the patient recovered or died. Most of these patients received parenteral fluids in the form of normal saline solution, 5 per cent glucose, blood transfusions and

amigen. In addition Wangensteen suction was instituted in many of these patients. Electrocardiograms (limb leads I, II and III and precordial leads CR_3, CR_4 and CR_5) were taken at the same time that blood samples were obtained. In five patients calcium in the form of

patients. In the five of the fifteen patients who had not received therapy prior to the initial estimation the serum potassium was also low. In general the level of serum potassium varied with the degree of alkalosis; the greater the degree of alkalosis the

TABLE II

SERUM LEVELS, CASE 15

J. G., aged twenty-five, diagnosis: ruptured duodenal ulcer.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Cl (mEq./L.)	CO_2 (mEq./L.)	Protein (Gm. %)	Blood Urea Nitrogen (mg. %)	Intake Record
2/5/48	2.7	147	4.7	72	39	5.7	150	3,000 cc. 5% glucose in saline 1,890 cc. tea and water orally
2/6/48	2.3	150	...	79	35	...	150	7:30 A.M., 1,000 cc. 5% glucose in saline
	3.7	...	...	98	34 before KCl 35 after KCl	...	105 before KCl 95 after KCl	10:30 A.M. 200 cc. 19% glucose in water From 7 to 4 P.M. 2,100 cc. tea orally, H_2O and jello 8 P.M. 500 cc. KCl 10 P.M. 700 cc. amino acids Clinically improved
2/7/48	2.7	142	4.0	80	31	...	90 12 hr. after KCl	2,000 cc. 10% glucose in H_2O 1,000 cc. 5% glucose in saline 1,000 cc. amigen 3,130 cc. tea and water Clinically improved
2/8/48	...	...	...	..	29	...	.....	Fluids orally 4,280 cc. tea and water
2/9/48	...	...	...	77	26	...	31	Fluids orally 3,780 cc. tea, H_2O, milk
2/10/48	4.5	140	4.7	..	26	...	39	Fluids orally 4,160 cc. tea, H_2O, milk; patient sitting up

10 cc. of 10 per cent calcium gluconate was injected intravenously prior to administration of potassium in order to determine whether deficiency of this ion was responsible for the electrocardiographic changes. In the series of patients with intestinal obstruction we satisfied ourselves that potassium, not calcium, deficiency was the cause of the electrocardiographic changes by showing that the serum calcium was not low and that intravenous calcium had no effect upon the electrocardiogram while serum potassium was low in five patients and its intravenous administration did return the tracings toward normal. The blood pressure was recorded at frequent intervals prior to, during and following administration of potassium.

The serum sodium and potassium concentrations were measured by means of the flame photometer.[15] (Tables I, II and III.)

FINDINGS

Serum Potassium and Other Electrolyte Values. The serum potassium on or soon after admission ranged between 2.3 mEq./L. and 2.5 mEq./L. in four patients and between 2.5 and 4.1 mEq./L. in eleven

lower the serum potassium. In practically all of these patients the serum potassium dropped to still lower levels following parenteral therapy which did not include potassium. The pertinent clinical findings, serum potassium levels, electrocardiographic findings on admission and the results of therapy are shown in Table IV.

The serum sodium, chloride and bicarbonate values in our series of patients differed in no way from the well known changes produced by vomiting due to intestinal obstruction. The resulting concentrations in the plasma depended upon the site of the intestinal obstruction (whether high or low), the duration and severity of the vomiting and the accompanying degree of dehydration. In general, in the presence of high intestinal obstruction the chief alterations observed were a marked diminution in chlorides, a slight or moderate diminution in sodium and an increase in carbon dioxide combining power with evidence of alkalosis. In low intestinal

obstruction there was moderate diminution in chlorides and, frequently, a marked loss of sodium with a tendency toward acidosis. The administration of parenteral fluids (saline and glucose) when the patient took no food by mouth resulted in an increase in chlorides, with a tendency for the degree of alkalosis to diminish. However, on administration of fluids which did not contain potassium the serum potassium tended not only to remain low but to fall below the initial values present on admission.

Of particular interest was the relationship between the level of the serum calcium and the serum potassium. When the serum potassium values were quite low (1.7 to 3.3 mEq./L.), usually associated with a considerable degree of alkalosis, the serum calcium levels also tended to be low but not nearly so low proportionately as the serum potassium. The serum calcium levels ranged between 3.5 to 4.5 mEq./L. in most of our patients when the serum potassium was low. This decrease involved the ionized as well as the unionized fraction.

Effect of Administration of Potassium on the Clinical State of Patient. Potassium chloride in the form of a 1.14 (isotonic) per cent solution was administered twelve times to ten patients. The dosage ranged from 100 to 700 cc. administered over a period of one-half to two and one-half hours. The effects upon the serum potassium are shown in Table v. Electrocardiograms were taken almost continuously during its administration in most of these patients. Following injection these patients in many instances showed evidence of clinical improvement as manifested by diminished weakness and a sense of well being. The blood pressure, usually low prior to injection, often rose 30 to 40 mm. Hg after potassium had been

TABLE III

SERUM LEVELS, CASE 10

J. McC., aged thirty-four, diagnosis, acute pancreatitis, pyloric obstruction.

Date	K (mEq./L.)	Na (mEq./L.)	Ca (mEq./L.)	Chloride (mEq./L.)	CO_2 (mEq./L.)	Remarks
12/29/47	3.6	140	...	..	51	
12/30/47	2.0	149	3.8			
12/31/47						
4:15 P.M.	2.8	147	4.5	..	35	After 200 cc. KCl
5 P.M.	2.8	142	4.6	76		
1/8/48	2.8	138	4.3	71	36	
1/9/48	3.6	132	4.8	83	38	
1/14/48						
12:30 P.M.	2.7	150	4.9	..	..	After 300 cc. KCl
2 P.M.	4.3	141	4.8			
1/15/48	3.5	138	...	76	24	
1/21/48	3.7	141	4.9	79	29	
2/5/48	2.4	144	3.9			
2/6/48	2.3	149	4.2			
2/7/48	2.3	147				
2/11/48	1.7	143	4.4	59	45	
2/12/48	2.3	130	4.4			
2/13/48	2.0	138	4.7	63	53	
2/16/48	1.9	...	6.7	69	45	
2/17/48	1.7	...	...	67	41	
2/18/48	1.7	146	...	66	56	
2/19/48	2.2	150	...	67	51	
2/20/48	2.3	142	3.7	70	50	
2/21/48	2.3	142	3.8	72	42	
2/22/48	2.0	141	3.8	71	36	
2/23/48	2.0	142	4.1	72	40	

TABLE IV

Case No.	Name	Age	Diagnosis	Vomiting (days)	Condition on Admission	Initial ECG	Initial Serum Potassium (mEq./L.)	Effect of Potassium on ECG and Serum Potassium	Ultimate Outcome
1 White Female	K. T.	70	Large bowel obstruction; strangulated femoral hernia	4	Dehydrated; weak	Prolonged QT; ST depression	2.4	Not given	Died
2 Negro	J. J.	57	Ulcer of duodenum with pyloric obstruction	4	Weak, comatose	Prolonged QT; ST depression	2.5	150 cc. in ½ hr.; decreased QT; ST returned to isoelectric line; K rose to 3.08 mEq./L.	Improved
3 White Female	C. L.	66	Cholecystitis; perforation of gallbladder; right subdiaphragmatic abscess	4	Acutely ill; abdominal distention; pain; rigidity of right upper quadrant	Prolonged QT; ST depressed	2.85	500 cc. of KCl in 1 hr.; K rose to 4.08 mEq./L. QT decreased, ST normal	Died
4 White Female	A. S.	72	Intestinal carcinoma with pyloric obstruction	1 wk.	Dehydrated; weak	Depressed ST; prolonged QT	3.6	Returned to normal	Signed out against advice
5 White Female	E. H.	65	Carcinoma of sigmoid with metastasis to liver	2	Dehydrated; weak; disoriented	Prolonged QT; depressed ST	3.4	Returned to normal	Discharged; condition improved
6 White Male	B. W.	68	Pyelonephritis with adynamic ileus	2	Dehydrated; weak; cyanosis; rapid pulse; shallow respirations; rigidity in abdomen; peristalsis	Inverted T wave with prolonged QT	3.3	Given 150 cc., T waves in CR_4 less inverted, K rose to 3.33 mEq./L.	Died
7 White Male	G. H.	61	Perforation of stomach due to ulcer; subphrenic abscess; generalized peritonitis with localization; arteriosclerotic heart	3	Fever; weakness	Depressed ST; prolonged QT	3.6	QT decreased; ST segment depressed; extrasystoles disappeared; K rose to 5.0 mEq./L.	Died
8 White Female	L.	61	Mentally defective; choledechotomy; removal of stone in common duct	?	Abdominal pain; dehydrated; clay-colored stools; icteric; tenderness in right upper quadrant	Depressed ST; prolonged QT	4.1	Returned to normal	Discharged improved
9 White Male	J. C.	76	Carcinoma of splenic flexure	1 wk.	Pain in lower abdomen; vomiting	Depressed ST; prolonged QT	2.9	QT returned to normal; ST depression disappeared; K rose to 5.13 mEq./L.	Improved
10 White Male	J. M.	45	Cysts of pancreas; pyloric stenosis	3 wk.	Dehydrated; weak	Depressed ST; prolonged QT	2.8	Short QT with upright T wave; after 200 cc. K rose to 2.95 mEq./L.	Improved
11 White Male	P. W.	63	Gastric carcinoma	3 wk.	Pain in upper abdomen; emaciated; not acutely ill	Prolonged QT; inverted T wave	3.2	Less T wave inversion; after 300 cc. K rose to 4.61 mEq./L.	Died after operation
12 Female	W. J.	51	Carcinoma of fundus; hysterectomy; shock after operation; parenteral fluid	2	Shock; dehydrated	Prolonged QT	2.4	Return to normal	Improved
13 White Female	C. W	42	Duodenal ulcer with pyloric obstruction	1 mo. also 1 to 2 watery stools per day	Dehydrated undernourished	Inverted T wave in all leads; long QT	3.8	Return to normal after 500 cc. K rose to 4.61 mEq./L.	Discharged improved
14 White Male	G. S.	87	Fracture of femur; intestinal obstruction	4	Dehydrated; weak	Prolonged QT; inverted T wave in all leads	3.9	Return to normal; after 500 cc. K rose to 6.66 mEq./L.	Discharged improved
15 White Male	W. G.	25	Ruptured duodenal ulcer	1	Shock; dehydrated	Low T_2 and U wave; long QT	2.3	Return to normal, after 500 cc. K rose to 3.2 mEq./L.	Improved

given. The diastolic pressure usually increased more than the systolic. The improvement was only temporary unless the cause for the potassium deficit was removed or the patient began to take food by mouth. In two of these patients (Cases 14 and 15) administration of potassium initiated improvement of the patient which was manifested by diminution of azotemia, a desire to take food by mouth, rapid return of the electrolytes to normal and recovery of the patient. The effects upon the electrocardiograph will be discussed presently.

Effect of Potassium Administration on the Level of Serum Potassium in Hypopotassemia. In Table II the effects of potassium chloride on the level of the serum potassium are noted. It will be observed that with small doses of potassium chloride, 125 to 150 cc., the rise in the level of the serum potassium at the end of administration was not very great. With larger doses (300 to 700 cc.) increase in the serum potassium level was greater and ranged up to 2.8 mEq./L. above the control level.

Effect of Administration of Potassium on Electrocardiogram in Hypopotassemia. Prior to administration of potassium the effect of intravenous administration of calcium gluconate (10 cc. of a 10 per cent solution) was noted. This had no appreciable effect on the T waves and the S-T segments in the five patients to whom this was given, thereby showing that the electrocardiographic changes were not the result of calcium deficiency. Following administration of potassium, the depression of the S-T segments diminished, the T waves tended to become or actually became upright and the Q-T segments were shortened in every case. (Figs. 1, 2, 3 and 4.) The degree of return to normal depended upon the degree of hypopotassemia present prior to injection and the amount of electrolyte administered. When small doses of potassium were given (100 to 200 cc.), only a partial return to normal occurred. With larger doses, a complete return to a normal tracing was observed. Extrasystoles which were present in five cases with low potassium were abolished following administration of this electrolyte.

The electrocardiographic improvement following administration of potassium was temporary in some patients; in others some degree of improvement persisted. In about one-half to three hours following administration the changes tended to revert to their previous configuration although in some instances some degree of improvement in the T waves and S-T segment was preserved. (Figs. 2, 3 and 4.)

TABLE V

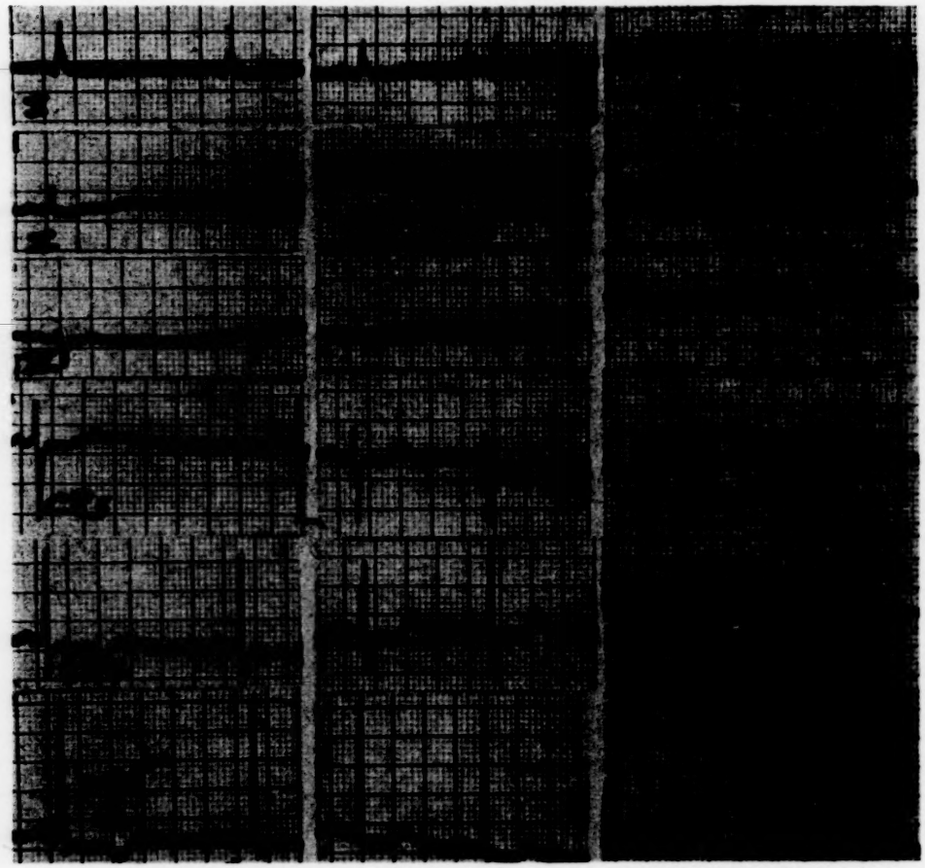
Case No.	Initial Serum Potassium (mEq./L.)	Quantity of 1.14 Per Cent Potassium Chloride per Unit Time Given	Serum Potassium at End of Administration (mEq./L.)
2	2.5	150 cc. in ½ hour	3.3
3	2.85	500 cc. in 1 hour	4.08
4	3.6	125 cc. in 1 hour	4.1
6	3.3	100 cc. in 1 hour	3.7
7	3.6	150 cc. in 1 hour	5.1
8	4.1	150 cc. in 1 hour	4.1
9	2.9	500 cc. in 2 hours	4.5
10	2.8	150 cc. in 1 hour	2.9
10	2.7	300 cc. in 2 hours	4.3
11	3.7	200 cc. in 2 hours	3.8
11	3.2	300 cc. in 2 hours	4.5
13	3.8	300 cc. in 2 hours	4.5
14	3.8	700 cc. in 3 hours	6.6
15	2.3	500 cc. in 2 hours	3.7

COMMENTS

A study of the literature together with an analysis of the data in our patients indicates that profound electrolyte disturbances are observed during acute intestinal obstruction. In addition to loss of water there is considerable depletion of body potassium. Marked diminution in body potassium results in precipitation of the syndrome of hypopotassemia. This electrolyte cannot be restored by administration of saline and glucose solutions and can be supplied only by direct administration or by food containing potassium.

RECOGNITION OF POTASSIUM DEFICIENCY

The diagnosis of potassium deficiency depends upon (1) recognition of the con-



1A 1B 1C

FIG. 1. C. L., a white patient aged sixty-six. A, electrocardiogram taken January 19, 1948, after the patient had been vomiting four days. Note inverted T wave in lead I, ST depression with prominent U wave in lead II and Lead III and inversion of the T wave in CR_4 and CR_5 with depression of the RT segment. The serum potassium at this time was 2.85 mEq./L. B, after 250 cc. of isotonic potassium chloride had been administered in a period of one hour and fifteen minutes. Note flattening of the T wave in leads I and II. Note that the T waves in CR_3, CR_4 and CR_5 are now upright. C, after 500 cc. potassium chloride had been given in two and one-half hours. Note flattening of the T wave in lead I with a tendency to an upright configuration, flattening of the T wave in lead II, with upright T waves in CR_3, CR_4 and CR_5. The potassium at this time was 4.08 mEq./L. The blood pressure rose from the control value of 100/80 to 120/90 after administration of potassium chloride.

ditions likely to be associated with this disturbance; (2) the presence of muscular weakness and atonic muscles and occasionally muscular paralysis; (3) characteristic electrocardiographic changes which return to normal when potassium is given; (4) confirmation by determination of the serum potassium. Particularly important is an estimation of the loss of body potassium by measurement of the retention of this electrolyte during the state of recovery.

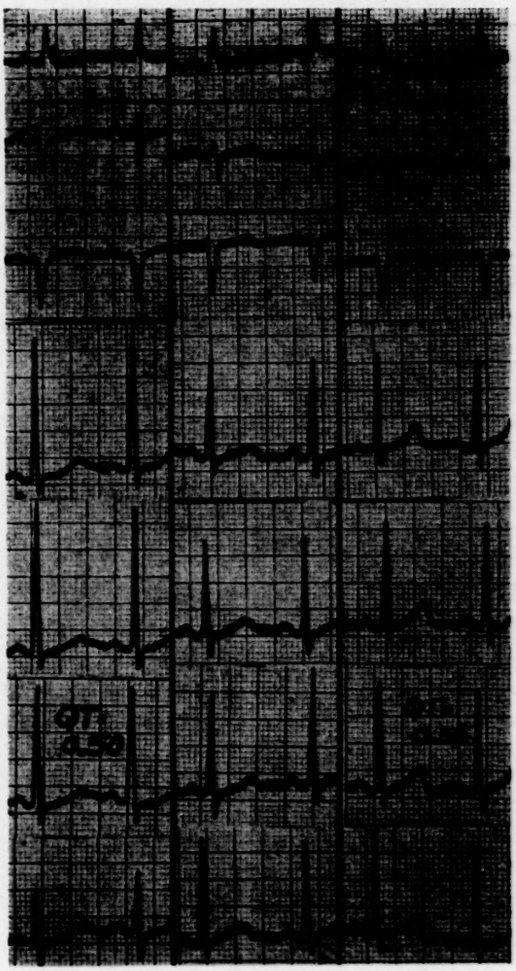
In man, hypopotassemia has been studied chiefly in familial periodic paralysis. In these patients muscle weakness, difficulty in respiration due to paralysis of the accessory muscles of respiration, general muscular paralysis and even death has been noted. More recently similar phenomena have been observed following therapy in diabetic acidosis and in chronic nephritis in which the serum potassium level may be as low as 2.0 mEq./L. While marked degrees of muscular paralysis are relatively uncommon accompaniments of potassium

deficiency, minor and moderate degrees of muscular weakness are common. In a recent paper Huang and Mao[16] describe eleven cases of transient paralysis occurring in patients with cholera on the second to ninth day after hospital admission. The paralysis was regarded as analogous to that developing in familial periodic paralysis and responded dramatically to the intravenous injection of potassium chloride. Unfortunately, the authors were unable to determine the level of serum potassium.

While no instance of frank muscular paralysis was observed in the patients in our series, varying grades of muscular weakness and asthenia were present. These were, in many instances, improved following administration of potassium. It is suggested that mild and moderate grades of muscular weakness and asthenia resulting from hypopotassemia are probably overlooked and attributed to the underlying clinical state.

The importance of potassium in the correct functioning of the isolated heart is well known and easily demonstrated. Deficiency of body potassium has produced necrosis of heart muscle in experimental muscle preparations. The following cardiac effects during hypopotassemia have been noted:[17–19] dilatation of the heart, development of systolic murmurs, ectopic rhythms and profound electrocardiographic changes of a type associated with severe grades of myocardial abnormalities. In addition the blood pressure is usually low. Such profound effects on the heart obviously add to the severity of the clinical picture. These alterations are usually promptly reversed by administration of potassium.

Since a deficiency of potassium affects many vital functions and since the potassium is depleted in intestinal obstruction, it seems very probable that some of the symptomatology of intestinal obstruction may be the result of a deficiency of potassium. This is based on the following: (1) the marked depletion of this important electrolyte in a relatively short period of time following vomiting; (2) the presence of asthenia, weakness, low blood pressure and a shock-like state which in many aspects resembles the syndrome of hypopotassemia; (3) the profound electrocardiographic changes; (4) finally administration of potassium results in improvement of the symptoms and signs with almost immediate restoration of the electrocardiogram to normal.



2A 2B 2C

FIG. 2. Case 10. Diagnosis: pyloric obstruction with cyst of pancreas. A, control, K 2.7 mEq./L. Note the low amplitude of the T waves in the precordial leads with lengthening of the Q-T interval to 0.50 second. B, forty-five minutes after 150 cc. of 1.12 per cent potassium chloride had been given. Note diminution of the RST segment depression with a slight increase in the amplitude of the T waves. C, two hours after 300 cc. of potassium chloride had been given. Note the further increase in the amplitude of the T wave. The Q-T interval now measures 0.236 second. The serum potassium at this time was 4.3 mEq./L.

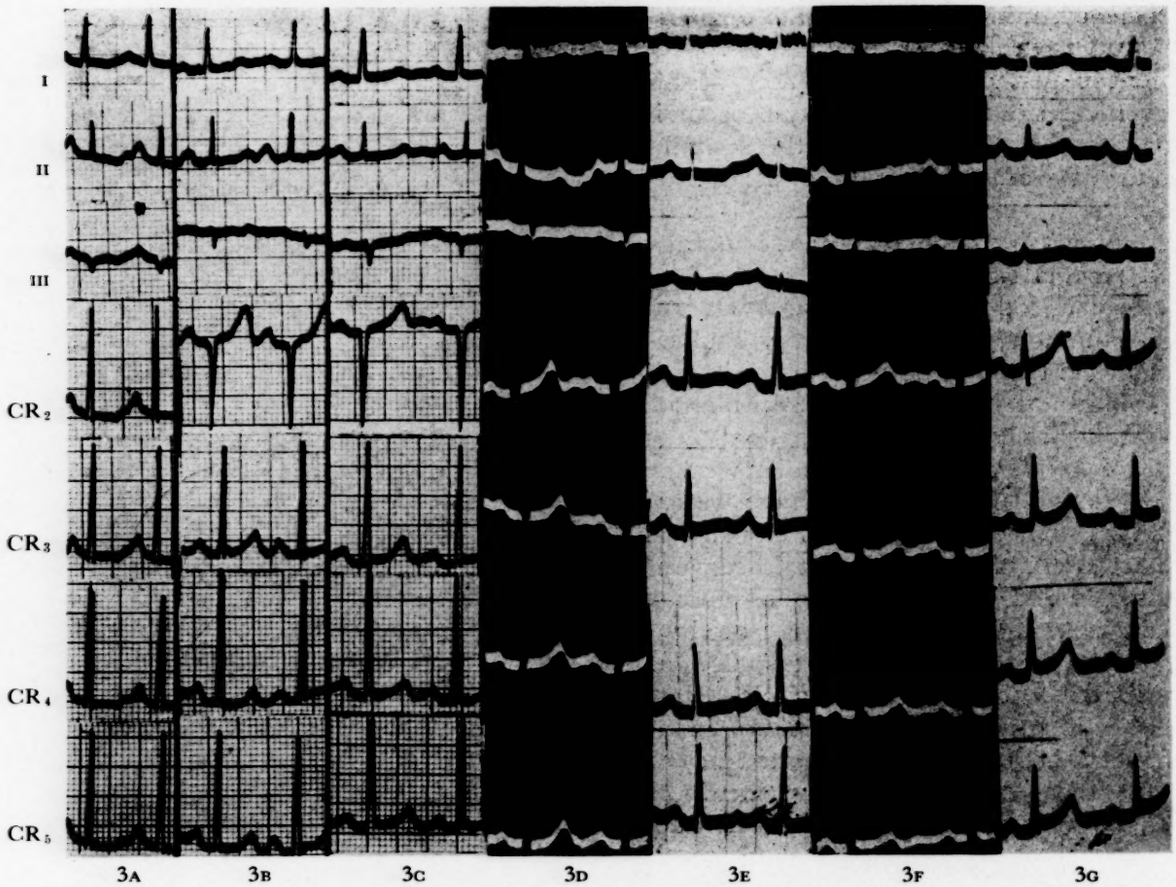
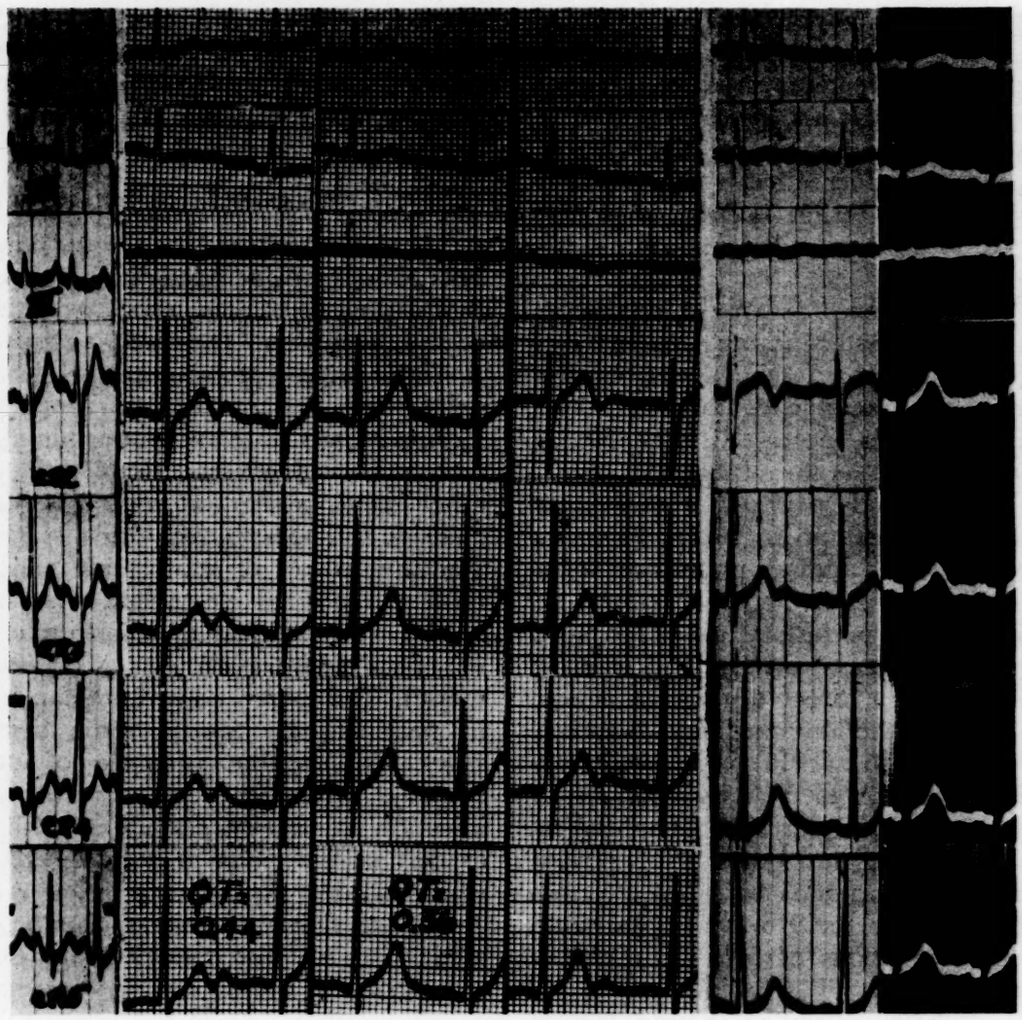


FIG. 3. Case 14, a patient aged eighty-seven. Diagnosis: lower intestinal obstruction due to carcinoma of the sigmoid. A, control, February 2, 1948. Potassium 3.8 mEq./L. Note inverted T waves in all leads with lengthening of the Q-T interval. B, after 150 cc. of potassium chloride had been given in forty-five minutes. The T wave is now upright. C, after 300 cc. had been given in two hours. Note the upright T waves. D, two hours after the potassium had been stopped the electrocardiogram shows no significant change. E, 3.24 hours later it shows flattened T waves in the precordial leads. F, after patient began to take food by mouth it shows a return of the serum potassium to normal with a more upright configuration of the T wave. G, February 7, 1948, shows continuing improvement with a practically normal electrocardiogram.

MECHANISM OF POTASSIUM LOSS THROUGH THE VOMITING PRODUCED BY INTESTINAL OBSTRUCTION

Potassium is lost in intestinal obstruction mainly through direct loss of the electrolyte which is present in the stomach and intestinal secretions. Long-continued vomiting of stomach secretions results in a loss of intra- and extracellular fluids which contain potassium and in the loss of potassium contained in the gastrointestinal secretions. Falconer[8a,d] observed that the vomitus contained five times the concentration of potassium present in the serum. Frenkel[17] found the potassium in vomitus to be from 40 to 50 mg. per cent. Austin and Gamman[20] observed that gastric juice contains two and one-half times as much potassium as is found in blood serum. With loss of gastric secretions containing free hydrochloric acid, more chloride is lost than sodium, with resulting production of alkalosis. The excess of sodium in proportion to chloride in such states may go into the cell, displacing potassium which is eliminated.

Loss of potassium may also result through procedures designed to treat the vomiting and certain other symptoms caused by intestinal obstruction. Suction by the Wan-



4A 4B 4C 4D 4E 4F

FIG. 4. Illustration of how parenteral fluids which contain no potassium help to produce and maintain low serum potassium levels. Case 15, a patient aged twenty-five. Diagnosis: ruptured duodenal ulcer; the patient vomited only one day prior to admission. A, January 30, 1948, prior to operation. Note tachycardia, upright T waves with slight depression of the S-T segments. Operation was performed (gastro-enterostomy). This patient was given fluids parenterally, saline and glucose, but was unable to take any food by mouth. B, February 6, 1948, control shows T waves to precordial leads of somewhat diminished amplitude followed by a second wave which resembles a U wave but may be part of a T wave (TU wave). The exact end of the T wave is difficult to determine. C, one hour and forty-five minutes after B, after 500 cc. of 1.2 per cent potassium chloride had been given; note increased amplitude of the T wave with absence of the U component of the TU wave. D, one hour later. Notice diminution in amplitude of the T wave with a small U wave. E, February 7, 1948, the patient had begun to take food by mouth earlier on this day. Note potassium to be 2.7 mEq./L. Note diminution of the U wave. F, February 10, 1948, the patient had been eating. The electrocardiogram is now relatively normal.

gensteen or Miller-Abbott tube results in the loss of large amounts of fluid which contain considerable amounts of potassium.

During periods of inanition there is a considerable loss of nitrogen from the cells. This also results in a loss of potassium which is present in the cells in a ratio of 2 Gm. of nitrogen to 1 mM. of potassium.

Parenteral administration of glucose tends to diminish the serum potassium, causing potassium to enter the cells of the muscles and liver in association with glycogen

formation. This is particularly apt to occur when the cellular potassium is low. In addition glucose tends to produce a transient depletion of salt and helps to eliminate potassium by production of diuresis. On the other hand, glucose has a sparing effect on protein loss which occurs when the patient is not taking food by mouth.

POTASSIUM AND CARDIAC FUNCTION

The action of potassium on the heart is a dual one, this ion affecting both impulse conduction and muscle contractility. The potassium ion is necessary for normal cardiac function; in the absence of potassium the isolated perfused mammalian heart will stop beating in systole. This can be corrected by adding potassium salts. On the other hand, if the concentration of potassium in the perfusion fluid is too high the heart will once again fail, this time in diastole due to a direct depressant action of the ion on the myocardium. Winkler, Hoff and Smith (1938)[21] administered potassium chloride to dogs by slow intravenous infusion and correlated changes in the electrocardiogram with the serum concentration of potassium. They found that alterations in the T wave appeared at serum concentrations of 5 to 7 mEq./L., depression of the S-T segment at 8 to 10 mEq./L., intraventricular block at 10 mEq./L., disappearance of P waves at 9 to 11 mEq./L. and cardiac arrest at 14 to 16 mEq./L.

The electrocardiogram serves as a fairly good criterion of serum potassium values. This is suggested by the following points: (1) The importance of potassium in muscle contraction, the electrical events of which are recorded by. the electrocardiogram; (2) the fact that the heart is the first organ to be affected by this drug following intravenous injection (even before skeletal muscle); (3) the almost immediate alterations in the electrocardiogram upon administration of small doses of potassium (as low as 50 cc. of isotonic potassium chloride); (4) the ability to follow the entire gamut of serum concentrations by the electrocardiogram from low to normal, high and toxic concentrations; (5) the failure to encounter typical electrocardiographic patterns of high or low potassium values in normal electrocardiograms.

THERAPEUTIC IMPLICATIONS

These findings indicate that potassium salts should be included in the parenteral fluids used in states associated with excessive vomiting. Darrow[22] suggests that the solution used to replace the electrolyte deficit should contain sodium chloride, sodium bicarbonate and potassium chloride when acidosis is present. In alkalosis, on the other hand, a solution containing sodium chloride and potassium chloride is indicated. The importance of establishing and maintaining a normal electrolyte balance cannot be over emphasized. Potassium chloride may be given intravenously, by clysis and by mouth. The intravenous route can be used in patients who are in some degree of shock and in the presence of diabetic acidosis. In other instances intravenous injection is usually associated with more or less severe pain at the injection site which renders its administration difficult. Administration by clysis is usually associated with no discomfort. Administration by mouth can be resorted to when feasible.

TOXICITY OF POTASSIUM

A discussion of the toxic effects of potassium is of importance because the therapeutic indications are to supply potassium in larger quantities to overcome the potassium deficit. Potassium chloride has been given by mouth in doses from 5 to 15 Gm. with no untoward effects to patients with normal renal function. Most of the potassium is eliminated in a period of three to four hours. The toxicity following parenteral injection depends upon the rapidity and amount injected, the potassium level prior to injection, the renal function and probably the condition of the heart at the time of injection. In man, in absence of potassium deficit, the maximum amount considered safe to inject intravenously at one dose is

only 3 to 4 mg./Kg. of body weight.[11,23] The chief danger in the use of potassium salts is the production of heart block. This develops when the extracellular concentration rises to a little more than twice the normal value. If renal function is good, potassium is rapidly excreted when the concentration in the serum rises. However, rapid intravenous administration can exceed the rate of excretion. Darrow[22] estimated that 3.5 mM. of potassium or 0.26 Gm. of potassium chloride per Kg. is a safe dose if used with proper precautions. The total dose should not be given in less than four hours and preferably should be given by slow drip in eight or more hours. For parenteral administration he suggests administration by hypodermoclysis since this method is safer than the intravenous route. Administration of potassium chloride should be combined with sodium chloride or sodium chloride and sodium bicarbonate together with intravenous glucose in water sufficient to supply the water requirement. The glucose probably facilitates the transfer of potassium to the cells.

In the patients of our group, all of whom had low levels of serum potassium and probably low cellular potassium, we injected quantities from 100 to 700 cc. of 1.14 per cent solution without untoward effect in a period of one to three hours. Our experience would tend to indicate that patients in a depleted state of potassium can tolerate large quantities without untoward effects. In case of doubt it is suggested that the injections be given slowly and frequent electrocardiographic checks be made before additional quantities are administered. It is believed that the dangers of potassium intoxication have been considerably overrated.

SUMMARY

1. The effect of severe vomiting upon the serum potassium level is discussed. The serum potassium was found to be low in fifteen patients with protracted vomiting and decreased still further following therapy with saline and glucose solutions. That the depletion involved not only the serum potassium but the intracellular potassium is suggested by the small rise in serum concentration following injection of relatively large doses of potassium chloride. The relationship of a low serum potassium to serum concentrations of other electrolytes is discussed.

2. The electrocardiographic patterns in hypopotassemia are described and the effects of administration of potassium are noted. The electrocardiogram is a fairly good criterion of potassium deficiency and of considerable importance in the diagnosis of this condition.

3. Administration of potassium resulted in clinical improvement in the patients described and in a return of the electrocardiogram to normal. Administration of this electrolyte in such states is important and in some patients may be life-saving.

Acknowledgments: The authors wish to thank Miss Claire Grobman and Miss Anne D. Arrison for their technical assistance.

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Hemodynamic Studies in Two Cases of Wolff-Parkinson-White Syndrome with Paroxysmal AV Nodal Tachycardia*

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Since the original description of Wolff-Parkinson-White syndrome,[1] a number of theories have been suggested to explain the abnormal electrocardiographic pattern and associated attacks of paroxysmal tachycardia. The concept of an accessory pathway similar to the bundle of Kent[2] represents the most acceptable explanation to date. The demonstration of the existence of such an anatomic atrioventricular connection in a patient known to present the characteristic clinical and electrocardiographic findings during life offers further evidence of the validity of the concept.[3] Pre-excitation of one ventricle with the typical Wolff-Parkinson-White electrocardiographic tracings has been produced experimentally previously;[4a,b] in addition, using the same pathway, supraventricular tachycardia was produced when conduction was retrograde from ventricle to auricle. This evidence provides a satisfactory explanation for many of the features of the anomalous conduction in this syndrome and suggests that the configuration of the QRS complex during the anomalous AV conduction could be explained by fusion from pre-excitation or by early excitation of one ventricle via the anomalous AV pathway and normal depolarization of the other ventricle by means of the normal conduction bundle and Purkinje system.

The theory of pre-excitation suggests the presence of ventricular asynchronism with the lag in ventricular contraction on the side opposite to the anomalous AV bundle. It has been shown[5] that the electrocardiographic pattern in Wolff-Parkinson-White syndrome may simulate both right and left bundle branch block, indicating an anomalous AV conduction pathway on the left or right side of the heart, respectively.

The manner in which the ventricle on the normal side is depolarized, however, is still uncertain. Originally it was believed that in most instances of Wolff-Parkinson-White syndrome excitation took place via the normal conduction pathway (His bundle and Purkinje system). Depolarization of this type would produce ventricular asynchronism characterized by a normal electrical-mechanical event relationship in the normal ventricle and an early onset of the mechanical event in the ventricle excited via the short-circuit pathway. In Kossman and Goldberger's patient[6] the anomalous pathway was probably located on the right side as evidenced by a left bundle branch block pattern. However, they found a considerable delay in onset of ejection into the carotid artery which suggests delayed left ventricular contraction. This would be unexpected if activation of the left ventricle occurred via the His bundle and Purkinje system. They believe,

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therefore, that the delay in contraction is dependent upon abnormal spread of activation through the left ventricular muscle mass and suggest the following sequence of electrical events: ventricular excitation occurred very early on the anomalous side and the excitation wave spread through the right ventricular muscle mass, across the I.V. septum to activate the left ventricular muscle mass before the excitation wave from the AV node traveling over normal specialized conduction pathways reached the left ventricular musculature.

The manner and sequence of ventricular activation may be further clarified by simultaneous registration of the electrical and mechanical events on both sides of the heart. Catheterization of the right ventricular chamber now makes this possible.

Although an abnormal AV pathway is present, it has been constantly stressed that the characteristics of this syndrome are found predominantly in adults without evidence of heart disease. Detailed investigation of the hemodynamics of the circulation in these patients would be of interest to rule out any subclinical cardiac abnormalities. In addition, little precise information is available concerning adaptation of the circulation in man to paroxysmal arrhythmias.

The present study consists in hemodynamic measurements made in two patients with all the characteristic features of the Wolff-Parkinson-White syndrome. Data concerning one of them has been discussed briefly in a previous publication.[7]

METHOD

Using the right heart catheterization technic, intracardiac, peripheral arterial and peripheral venous pressure tracings were recorded by means of Hamilton manometers and were registered simultaneously with the electrocardiogram in two patients with Wolff-Parkinson-White syndrome. A Cambridge instrument of the string galvanometer type was used for inscription of the electrocardiogram. The time lag in mechanical transmission of an impulse through the catheter has been found to be 0.01 second.[8] Cardiac output, using the direct Fick principle, was also measured and peripheral vascular resistance and stroke volume were computed. These data were obtained during the anomalous atrioventricular conduction and also during an attack of supraventricular tachycardia in each of the two subjects. One patient (G. F.), a woman of twenty-nine, had no evidence of organic heart or pulmonary disease. The other (K. N.), a male of forty-one, had pulmonary tuberculosis, a left thoracoplasty and some disturbance in pulmonary function. Both were subject to spontaneous attacks of tachycardia. In one patient (G. F.) exploration of the right heart chambers, using a direct intracardiac lead placed in one side of a double lumen catheter,* permitted the electrocardiographic registration of intracavitary potentials simultaneously with the intracardiac pressure curves. The central terminal of Wilson was used as the indifferent electrode in this instance.

ELECTROCARDIOGRAPHIC DATA

The electrocardiograms taken before catheterization in both cases show the short PR and prolonged QRS intervals characteristic of the syndrome. In one patient (G. F.) a series of unipolar precordial leads, using Wilson's central terminal, and the three augmented unipolar limb leads were taken and show a pattern similar to left bundle branch block with delayed activation over the left side of the heart, suggesting a right bundle of Kent. In the second patient (K. N.) the QRS complexes in the standard leads are similar to the right bundle branch block pattern, indicating a left Kent bundle.

Introduction of the venous catheter into the right auricle in each case was followed by production of a paroxysmal supraventricular tachycardia with a ventricular rate of 187 and 178, respectively. Identification of the location of the ectopic pacemaker was difficult in one patient (G. F.) until the registration of the intracardiac (intraauricular) pattern identified it as AV nodal in origin, with a retrograde P wave falling after the descending limb of the R

* This catheter was supplied by the United States Catheter & Instrument Corp., Glens Falls, N. Y.

FIG. 1. Records taken during nodal tachycardia in patient G. F. Simultaneous records are shown of the brachial artery (B. A.) pressure and the intracardiac lead with the right atrial, superior vena cava and subclavian vein pressure tracings. The standard leads I, II and III of the electrocardiogram are also shown. Note the markedly abnormal pressure tracings in the right atrium (RT. AT.) and superior vena cava (SUP. VENA CAVA) and the changing character of the intracardiac lead as it was displaced from auricle to subclavian vein. The retrograde P wave (P) is well seen in the auriculogram.

wave. (Fig. 1.) In addition the auricular pressure curves, to be discussed later, proved to be characteristic of this particular arrhythmia as shown by Lewis.[9] In the second patient (K. N.) no intracardiac lead was available but auricular pressure curves obtained during the supraventricular tachycardia were identical with those of the first patient. This fact plus the electrocardiographic evidence in the standard leads makes the diagnosis of AV nodal tachycardia in this case most likely.

HEMODYNAMIC DATA

Data obtained in the two patients are tabulated in Table I. For comparison average values obtained in normal subjects are also presented.

During Nodal Tachycardia. In both cases during nodal tachycardia the changes in hemodynamics followed the same pattern. This tachycardia was characterized by a retrograde P wave identified by the intracardiac lead. (Fig. 1.) There was, however, a marked alteration of pressures in the right auricle, superior vena cava and, to a lesser degree, in the subclavian vein (Fig. 1 and Table I) as compared with the normal tracings. (Fig. 2 and Table I.) The contour of the abnormal pressure curves in the auricle during nodal tachycardia are identical to those in the jugular tracings described by Lewis[9] who considered them to be combination A and C waves. The curves in the superior vena cava resemble those in the right auricle very closely. Jugular vein tracings would, no doubt, approximate those in the superior vena cava since there is no valve between these two venous channels. There is a striking difference, however, in the tracings taken in the subclavian vein, largely because a competent venous valve separates this vein from the innominate. This is evidenced also by the large pressure difference between the superior vena cava and subclavian vein. In spite of the dampening effect of this valve on the pulse wave as it travels through the large intrathoracic veins, a sharp rise in pressure appears corresponding to the rise in pressure in the right auricle. Comparison of the mean pressures in the right auricle during Wolff-Parkinson-White conduction and nodal tachycardia (Table I) demonstrates the considerable increase in pressure during tachycardia. During aberrant conduction the right atrial mean pressure was 2.0 mm. Hg (27 mm. of water) and during nodal tachycardia the mean pressure rose to 8.0 mm. Hg (109 mm. of water). The peaks of pressure rise actually reach 20 mm. Hg (272 mm. of water) while normal auricular systole rarely exceeds 5 mm. Hg (68 mm. of water). This peak pressure rise approaches the normal right ventricular systolic pressure level. (Table I and Fig. 1.)

Onset of the auricular pressure rise during tachycardia occurs 0.11 second after

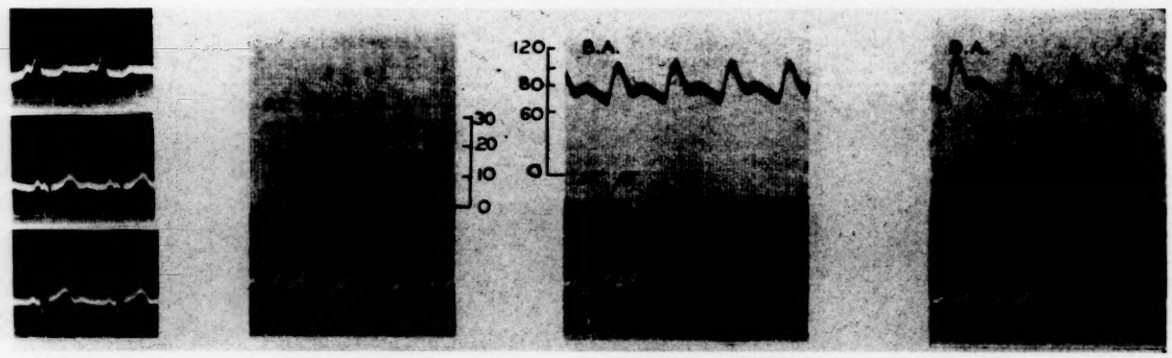

FIG. 2. Records taken during Wolff-Parkinson-White conduction in patient G. F. The blood pressure records were taken in the right ventricle (RT. VENT.), the brachial artery (BA), the right atrium (RT. AT.) and the subclavian vein (SUBCLAV. V.). Many artefacts are seen in the tracings from the right ventricle and atrium; the pressures, however, appear essentially normal.

the beginning of the QRS complex and precedes in time the electrocardiographic inscription of the retrograde P wave which falls after the descending limb of the QRS complex. (Fig. 1.) Normally the onset of ventricular systole, as recorded in the auricular pressure tracing, occurs 0.06 to 0.09 second after the beginning of the QRS. The abnormally high upward deflection in the auricular pressure wave simulates a ventricular pressure curve and has lost the normal A, C and V waves. This abnormal pressure rise in the right auricle is probably due to the summation of two events: (1) regurgitation of blood through the tricuspid valve during ventricular isometric contraction and early ejection and (2) auricular systolic contraction following the retrograde P wave. Both events occurring in rapid succession would be inscribed as a single upward deflection of marked amplitude. The cause of the tricuspid regurgitation is probably to be ascribed to the absence of a normal auricular systole

TABLE I

HEMODYNAMIC STUDIES IN TWO PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME AND NODAL TACHYCARDIA

Patient	Pulse Rate	Blood Pressures in mm. Hg						Cardiac Output		Peripheral Resistance Dynes cm.$^{-5}$ sec.
		Brachial Artery		Right Ventricle (Syst./Diast.)	Right Atrium (Mean)	Superior Vena Cava (Mean)	Subclavian Vein (Mean)	L./min./m^2	Per Beat	
		(Syst./Diast.)	(Mean)							
Normal	...	120/70	90	28/2	1	1	4	3.12 ± 0.4	50–90	1500
G. F.										
Nodal tachycardia	187	102/73	80	....	8	7	5	3.39	27	1130
W-P-W conduction with right bundle of Kent	78	104/66	77	28/3	2	..	3	3.16	60	1240
K. N.										
Nodal tachycardia	178	105/77	90	....	6	..	..	2.30	24	1600
W-P-W conduction with left bundle of Kent	121	104/72	84	32/1	1	−1	−1	2.29	34	1590

occurring near the end of ventricular diastole. The role played by auricular systole in the closure of the AV valves has been emphasized by many authors. According to Wiggers,[10] production of turbulent flow with formation of eddies tends to close the valves. In addition an area of negative pressure develops in the axial stream when the jet of blood is suddenly stopped at the end of auricular systole. Into this area of negative pressure blood is drawn from the sides "much as water in the wake of a ship" and the valves are carried with the blood and approximate their leaflets.

As in nodal tachycardia the auricular systole follows the onset of ventricular systole, these mechanisms for the valve leaflet approximation are not operating at the proper time in relation to ventricular systole. Furthermore, mechanical auricular systole occurs against a closed tricuspid valve since the ventricle is contracting and intraventricular pressure is high. The very high peak of auricular pressure probably favors retrograde flow into the intrathoracic venous system as far as the peripheral venous valves during part of the cardiac cycle. Thus auricular filling which normally takes place during ventricular systole is inadequate because of retrograde flow and abnormally high auricular pressures. The filling of the auricles is therefore limited to the very short interval during which the auricular pressure is falling and the filling of the right ventricle during the short period of diastolic inflow is probably inadequate.

It is not surprising, therefore, that the cardiac output during tachycardia remains unchanged as compared to the cardiac output during Wolff-Parkinson-White conduction and normal rhythm and that stroke volume is considerably reduced. It should be emphasized that the cardiac output was determined fifty minutes after the onset of nodal tachycardia and it is impossible to predict how long the systemic flow would remain at that level.

It has been just noted that the mean pressure in the subclavian vein is lower than in the large veins of the thorax, a situation somewhat different from that arising in the usual type of tricuspid insufficiency[11] with right ventricular and auricular dilatation associated with large blood volumes and cardiac failure. The peripheral venous flow in the arm must therefore be discontinuous, taking place only after the large retrograde wave moving from the auricle into the large vessels of the thorax has passed. As is well known clinical observation of jugular venous pulsations provides in these arrhythmias more information than measurement of the peripheral venous pressure.

In an attempt to secure right ventricular pressure tracings during nodal tachycardia in both cases the catheter was advanced from the right auricle into the right ventricle. This maneuver broke the nodal tachycardia in both patients. In one (G. F.), a continuous electrocardiogram was recorded during movement of the catheter and resumption of normal sinus rhythm with Wolff-Parkinson-White conduction was preceded by a premature ventricular systole.

During Wolff-Parkinson-White Conduction. During normal sinus rhythm with Wolff-Parkinson-White conduction the hemodynamics of the circulation in one patient (G. F.) were entirely normal. The cardiac output, peripheral vascular resistance and arterial blood pressures were the same as during tachycardia (Table 1) but right auricular and subclavian vein mean pressures were lower. The right ventricular pressures were within normal limits. (Table 1 and Fig. 2.)

The second patient (K. N.) had a low cardiac output and a slightly elevated right ventricular systolic pressure during sinus rhythm with Wolff-Parkinson-White conduction. (Table 1.) These findings are compatible with the diagnosis of early cor pulmonale related to chronic pulmonary disease and collapse of one lung by thoracoplasty. Arterial blood pressures and peripheral vascular resistance were normal and the same as when measured during nodal tachycardia. The right ventricular

diastolic and right auricular mean pressures were within normal limits and the latter was considerably lower than during the arrhythmia. Stroke volume increased but was still low during aberrant conduction. This resulted from the dual effect of low cardiac output and sinus tachycardia. (Table I.)

TABLE II

ELECTROCARDIOGRAPHIC DATA AND ELECTRICAL MECHANICAL INTERVALS IN TWO PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

Patient	Pulse Rate	Electrocardiographic Data. (sec.)		Electrical Mechanical Intervals, (sec.)		
		PR Interval	QRS Interval	P-At_s	Q-RV_s	Q-BA_s
Normal	60–100	0.12–0.20	0.06–0.10	0.05–0.11	0.06–0.09	0.14–0.19
G. F.						
Nodal tachycardia	187	.....	0.06	.....	.....	0.18
W-P-W conduction with right bundle of Kent	78	0.08	0.12	0.08	0.10	0.24
K. N.						
Nodal tachycardia	178	.....	0.08	.....	.....	0.19
W-P-W conduction with left bundle of Kent	121	0.11	0.12	0.06	0.16	0.24

In summary, a comparison of the hemodynamic data obtained during Wolff-Parkinson-White conduction and during paroxysmal nodal tachycardia in these two patients shows that during the latter: (1) the cardiac output was unchanged with the development of striking pressure abnormalities in the right auricle and despite marked increase in ventricular rate, (2) the stroke volume was greatly diminished and (3) the arterial blood pressure and peripheral vascular resistance were not altered.

ELECTRICAL-MECHANICAL EVENTS

It is generally agreed that there is no abnormality in auricular activation in Wolff-Parkinson-White syndrome. The basic disturbance appears to be abnormal ventricular excitation. An analysis of the time intervals between electrical and mechanical events in the cardiac cycle was undertaken in order further to elucidate this problem. In considering the abnormal electrical-mechanical relationship seen in these two patients (Table II) during aberrant AV excitation and nodal tachycardia, comparison with normal intervals (Table II) is essential. Three time intervals are to be considered: (1) the time interval between the beginning of the P wave and the onset of auricular systole (P-AT_s), (2) the time interval between the beginning of the initial deflection of the QRS complex (Q) and the onset of right ventricular systole (Q-RV_s) and (3) the time interval between the beginning of Q and the onset of pressure rise in the brachial artery (Q-BA_s). This latter gives indirect information as to the contraction of the left ventricle. No attempt has been made to delineate the relationship in time of diastole to the electrical events.

During Nodal Tachycardia. In both patients during the AV nodal tachycardia it was impossible to determine the P-AT_s time interval because of the distorted pressure curve and the presence of a retrograde P wave. No information is available concerning events in the right ventricle during the arrhythmia since passage of the catheter into this chamber interrupted the tachycardia and restored the aberrant conduction and sinus rhythm. From analysis of the relationship of electrical-mechanical events in the brachial artery (Table II) it can be

seen that the Q-BA$_a$ time during tachycardia was normal in both cases. At this time presumably depolarization of both ventricles was accomplished via the normal conduction system as evidenced by the normal QRS interval (Table II) of 0.06 and 0.08 second, respectively.

During Wolff-Parkinson-White Conduction. During Wolff-Parkinson-White conduction and sinus rhythm the electrical-mechanical event relationship in the right auricle, as expressed by the P-AT$_a$ interval, was normal in both patients.

Analysis of the ventricular events, however, reveals similar abnormalities in both patients. These are characterized by prolongation of both the Q-BA$_a$ and Q-RV$_a$ intervals, indicating a delay in the onset of the systole in both the right and left ventricles. It seems evident that neither ventricle is activated by the normal conduction pathways. Rather it is likely that the ventricular excitation wave is conducted entirely via muscular tissue. Since the velocity of impulse transmission is slower in muscle (approximately 400 mm./sec.) than in specialized conduction tissue (4,000 mm./sec.),[9] prolongation of the Q-BA$_a$ and Q-RV$_a$ intervals is compatible with the theory that the short circuit pathway carries the impulse directly into ventricular muscle mass, depolarization then spreading through both ventricles by muscular pathways. A necessary corollary to the theory of muscular conduction in both ventricles during anomalous excitation is that the accession wave traveling over the normal conduction system on the contralateral side arrives to find the normal ventricle already partially depolarized and therefore refractory. Marked prematurity of conduction to the ventricle via the anomalous bundle[6] or relative prolongation of the delay at the AV node of the normal electrical activation,[5] or both, would permit the pre-excitation wave to reach the I.V. septum and activate the normal side before the arrival of the normally progressing impulse. This would occur provided the terminus of the aberrant AV bundle is not too far from the interventricular septum. Mahaim[12] has identified and stressed this particular location of an accessory pathway. Consideration of the electrical-mechanical events in each case supports this theory.

In the patient (G. F.) with an electrocardiographic pattern similar to left bundle branch block and suggesting a right bundle of Kent, the onset of systole is markedly delayed on the left or normal side of the heart, as evidenced by a prolonged Q-BA$_a$ time interval (Table II), while the Q-RV$_a$ interval is only slightly prolonged. The marked lengthening of the Q-BA$_a$ time interval and the delayed activation over the left side of the heart in the precordial leads suggest that the impulse reaches the left ventricle only after initial activation of the right.

In the patient (K. N.) who had a right bundle branch block pattern and presumably a left bundle of Kent the onset of systole was markedly delayed in both ventricles as evidenced by prolonged Q-RV$_a$ and Q-BA$_a$ time intervals. (Table II.) The lengthening of these time intervals can be explained by an aberrant AV conduction into the base of the left ventricle with subsequent activation of both ventricles by spread of the impulse through left ventricular muscle mass, interventricular septum and right ventricular muscle mass. However, both patients had identical Q-BA$_a$ time intervals although in one the aberrant bundle was opposite in location to the other. If one assumes that it requires approximately 0.04 to 0.06 second[6] for an impulse to travel from one ventricle to the other, as is the case in patients with true bundle branch block, then the patient (G. F.) who had a right aberrant bundle may have ventricular asynchronism entirely due to late activation of the lagging left ventricle. In the patient with a left anomalous pathway (K. N.) the delay on the right side is easily explained by the time required for the impulse to reach and to stimulate fully the right ventricle. The delay on the left side, however, is as great as on the right. If it requires 0.05 second to activate com-

pletely the thicker ventricle, even though the impulse reaches it first in this patient, it is difficult to see why the Q-BA_v time in the first patient (G. F.) is not longer since the impulse starts from the right ventricle in this instance and must travel over to the left. It may be that the location of the distal end of the aberrant pathway is sufficiently variable in patients with the bundle of Kent on the same side to account for entirely different sites of origin of the initial ventricular excitation as well as different sequences of depolarization. If in the patient with a right Kent bundle (G. F.) the bundle is long and the terminus lies near the interventricular septum, the excitation wave would spread in opposite directions and depolarization begin at nearly the same time in each ventricle. The difference in delay on each side, therefore, would be largely a matter of ventricular thickness. If the bundle is short and the terminus in the second patient lies near the base of the left ventricle, the pathway taken by the excitation wave would be more circuitous and the delay in the left ventricular mechanical event would be due to slow progression of the wave through a thick wall. Delay on the right would result both from the late arrival of the impulse on that side and delayed progression of electrical stimulation through the thinner right ventricular wall. With a cor pulmonale, the increased right ventricular muscle mass might further prolong the Q-RV_v. The net result in this instance would be a nearly synchronous contraction of both ventricles.

In summary, the data obtained by analysis of electrical-mechanical events in this syndrome suggests that the anomalous bundle is probably located on opposite sides of the heart in each patient. There is probably abnormal activation of both ventricles in each case, due in large measure to exclusive muscular conduction of the excitation wave. Ventricular asynchronism may and probably does exist in one patient and is probably absent in the second patient because of: (1) differences in location of the terminus of the aberrant pathway with resultant alteration of the sequence of depolarization and (2) differences in thickness of the two ventricles.

INTRACAVITARY POTENTIALS

In one patient (G. F.), using the intracardiac electrode, intracavitary potentials were recorded during nodal tachycardia and sinus rhythm with Wolff-Parkinson-White conduction.

During nodal tachycardia, as can be seen in Figure 1, with the electrode in the auricle the QRS complex probably consists of a small initial positive deflection (R) followed by a deep negative deflection (S) and small final positive wave (R′). Immediately following the QRS complex there is a biphasic rapid deflection characterizing the retrograde P wave. When the intracavitary electrode was located in the superior vena cava the ventricular complex no longer showed an initial positive deflection. The retrograde P wave has almost entirely lost its biphasic character. The pattern recorded in the subclavian vein no longer shows any P wave and the negative T wave is now discernible.

Standard leads in this patient show supraventricular tachycardia. Further identification of the origin of the arrhythmia was made possible only by location of the retrograde P wave in the auriculogram.

During Wolff-Parkinson-White conduction with presumably a right accessory pathway, the intracavitary potentials recorded in the right ventricle in G. F. (Fig. 2) were characterized by an upright P wave and a QRS which begins with a small positive deflection (R) followed by a rapid but small S wave and a large final R′. The T wave is upright and there may be a small U wave which follows it. The auriculogram showed the expected variation of the P wave with different positions of the electrode. When the electrode was near the tricuspid valve (Fig. 2) in about the mid-auricular position, the ventricular deflections consist of a large negative followed by a large positive component. The T wave is difficult to delineate. With the electrode high in the auricle, near the

SA node, the QRS consists of R, S and R′ with a positive T wave.

The ventriculogram does not resemble those seen with classical left bundle branch block.[13,14] There appears to be no current of injury to distort the curve. However, the QRS does not have the usual right ventricular pattern of a small R and a deep S[13,14] reported as normal. Insufficient knowledge concerning the different patterns that may be found in normal right ventricles precludes further interpretation of the intracavitary potentials in this patient.

SUMMARY AND CONCLUSIONS

Using the right heart catheterization technic, intracardiac and peripheral arterial and venous pressure tracings were recorded simultaneously with the electrocardiogram in two patients with Wolff-Parkinson-White syndrome. Cardiac output, peripheral resistance and stroke volume were also measured. These data were obtained during the anomalous atrioventricular conduction and also during an attack of supraventricular tachycardia in each of the two patients.

In one case exploration of the right heart chambers, using a direct intracardiac lead, permitted the electrocardiographic registration of intracavitary potentials simultaneously with the intracardiac pressure curves. In this case identification of the supraventricular tachycardia as nodal could only be made in the intracardiac lead tracing.

The information obtained in these two patients suggests that the anomalous conduction pathway was located on different sides of the heart in each patient and that ventricular excitation was not normal in either ventricle during aberrant conduction.

Hemodynamic studies during the first fifty minutes of the nodal tachycardia demonstrate that there were marked pressure and presumably filling abnormalities in the right auricle related to tricuspid insufficiency and an auricular systole abnormal in time. With these alterations and despite the increased rate, the cardiac output was unchanged.

During Wolff-Parkinson-White conduction and sinus rhythm, intracardiac and arterial blood pressures and systemic flow were normal in one patient. Abnormalities in these values found in the other patient could be ascribed to a coincident early cor pulmonale.

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Studies on Coronary Circulation*

V. Quantitative Changes in a Serum Mucoprotein Following the Occurrence of Myocardial Infarction

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THE diagnosis of myocardial infarction is not infrequently a difficult one, especially in cases in which the electrocardiographic changes are absent, minimal or atypical. In these situations laboratory procedures such as the sedimentation rate and white count, which are commonly used as diagnostic aids, may be of little value because of the non-specificity of these tests. With these facts in mind, it was postulated that an approach could be made to a more accurate diagnosis of myocardial infarction if substances derived from the breakdown of infarcted heart muscle could be detected and measured in the blood or urine of such patients.

Since the breakdown of infarcted heart muscle by proteolytic enzyme activity could conceivably result in the release of cardiac muscle proteins and their breakdown products into the blood, it was thought that investigation of serum protein changes following myocardial infarction would be of interest. The previous work of Winzler and Burke[1] and the continuing studies of Winzler[2] on serum proteose changes in animals and man with cancer attracted our attention to study of the quantitative change of this serum component following the occurrence of myocardial infarction. Although this material was originally designated as a proteose because it is heat-stable, perchloric acid soluble, non-dialyzable and can be salted out with saturated ammonium sulfate,[3] further studies on the chemical and physical properties of this material by Winzler[2] indicate that it may be classified more properly as a mucoprotein. Therefore, this communication constitutes a study of the quantitative changes in a serum mucoprotein following the occurrence of myocardial infarction in man. Although an increase in the serum concentration of this mucoprotein following myocardial infarction cannot be considered specific for this condition, as originally hoped, this procedure has nevertheless proved helpful as a diagnostic aid under certain circumstances.

METHOD AND MATERIALS

Principle. The method for determination of the serum mucoprotein component† studied here was adapted from the procedure recently developed by Winzler and his associates.[3] It is based upon the fact that this material is not precipitated by 6 per cent perchloric acid which does, however, precipitate the other serum proteins. Following removal of the serum proteins by perchloric acid, the mucoprotein which has remained in solution is precipitated by phosphotungstic acid, and the precipitate is quantitatively measured by the biuret or tyrosine color reactions. In this study the biuret color reaction was used for determination of serum mucoprotein.

Details of Method. To an exactly measured volume of serum, preferably 6 ml. obtained from 15 to 20 ml. of clotted blood, is added a solution of 6 per cent perchloric acid in an amount which is twice the volume of the serum sample. The mixture is shaken well and allowed

† For the sake of convenience this material will be referred to as "serum mucoprotein" throughout the rest of this paper.

* From the Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles, Calif. Endowed by grants from the Blanche May and Beaumont Trust Funds.

to stand ten minutes. A heavy whitish-yellow precipitate forms. At the end of ten minutes the solution is filtered, using No. 50, 9.0 cm. Whatman filter paper. The time required for complete filtration varies from forty-five minutes to two hours. The filtrate should be clear and colorless; if any turbidity is seen, it should be refiltered through the same filter until clear. Exactly 10 ml. of the filtrate, measured with a 10 ml. volumetric pipet, is placed in a 15 ml. centrifuge tube and 2 ml. of 5 per cent phosphotungstic acid in 2 N HCl is added. A flocculent precipitate is formed. The solution is gently agitated and allowed to stand for ten minutes. The precipitate is separated by centrifugation for ten minutes. The clear supernatant is decanted and the precipitate is washed with 5 ml. of 5 per cent phosphotungstic acid in 2 N hydrochloric acid. After centrifugation the supernatant is again decanted.

The precipitate is dissolved in exactly 5 ml. of 0.2 N sodium hydroxide. At the same time a blank tube is prepared with 5 ml. of 0.2 N sodium hydroxide and a standard tube with 5 mg. casein in 5 ml. of 0.2 N sodium hydroxide. One ml. biuret reagent* is added to the blank, the standard and the unknown sample. The tubes are placed in the dark for one hour to permit full color development. At the end of an hour the color in the tubes is read with a Klett-Summerson Photoelectric Colorimeter using a green filter No. 54.

The serum concentration of this material may be calculated by the following formula:

$$\text{Mg. mucoprotein per 100 ml. serum} = \frac{\dfrac{\text{Colorimetric reading of unknown}}{\text{Colorimetric reading of standard}} \times 5 \text{ mg. casein} \times 100}{\dfrac{\text{Volume of filtrate used for determination}}{\text{Total volume of filtrate}} \times \text{volume serum}}$$

Normal mucoprotein values ranged from 40 to 90 mg. per 100 ml. of serum. These values which were obtained in this laboratory correlated well with those found by Winzler.[3]

Serial serum mucoprotein determinations were performed on twenty-three patients in whom the diagnosis of a recent myocardial infarction was made and subsequently was confirmed by either electrocardiographic changes or pathologic examination of the heart. The usual procedure was to determine the serum mucoprotein level twice a week for the first two weeks and then once weekly thereafter for the duration of the hospital stay. All patients were hospitalized and practically all of the blood samples were obtained between 9 and 11 A.M. In a few patients serum mucoprotein levels were obtained two to four months after onset of the illness at a time when satisfactory convalescence from the acute episode had been brought about. The corrected Wintrobe sedimentation rate[4] was obtained each time a mucoprotein determination was made. In a few instances the Linzenmeier sedimentation rate[5] was taken. Serum mucoprotein levels were correlated with sedimentation rate, leukocyte count, body temperature of the patient and the patient's clinical status. In this series there were eight deaths. Autopsy was performed on two of these patients and in both instances the clinical diagnosis was confirmed.

Serum mucoprotein levels were also determined in a second series of twelve patients who complained of prolonged chest pain and in whom it was at first difficult to tell whether or not a recent myocardial infarction had occurred. There were patients in this group who had angina pectoris, paroxysmal tachycardia, fibrositis and pain of psychogenic origin.

Serum mucoprotein levels were determined in a third group of twenty-six hospital patients with miscellaneous non-cardiac illnesses.

RESULTS

Serum Mucoprotein Changes in Myocardial Infarction. In all but two of the twenty-three patients with a proven diagnosis of myocardial infarction there was a clearcut rise in the serum mucoprotein level. It was found that a characteristic rise and fall of serum mucoprotein occurred following the clinical onset of the disease. (Fig. 1.) The peak of the rise in serum mucoprotein exceeded the value considered as the upper limit of normal in all but three instances. In

* Composition of biuret reagent: 500 mg. $CuSO_4 \cdot 5H_2O$, 5 ml. 28 per cent ammonium hydroxide, 85 ml. 40 per cent carbonate-free sodium hydroxide diluted to 100 ml. with distilled water.

this series the actual rise in mucoprotein above each patient's normal value varied from 22 to 160 mg. per 100 ml. A tabulation of the results obtained for each patient may be seen in Table 1.

It was found that serial determinations first two days. For example, in this series there were mucoprotein levels above the range of normal in five of eight determinations performed on patients during the first two days. The peak of the rise in mucoprotein occurred on the fifth and sixth days.

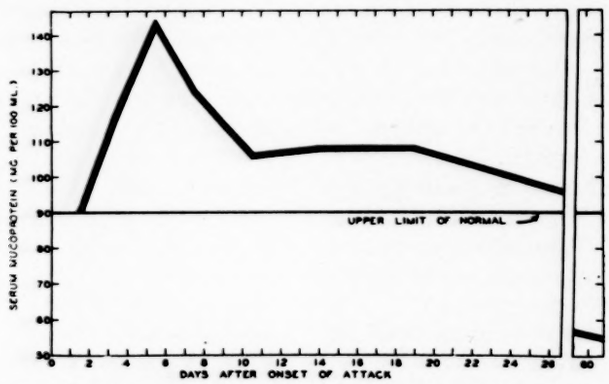

FIG. 1. Curve illustrating serum mucoprotein response following myocardial infarction. This curve is based upon the average serum mucoprotein values of the twenty-three cases listed in Table 1.

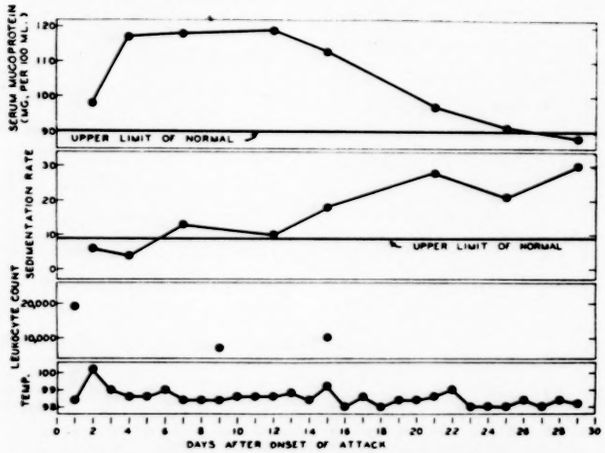

FIG. 2. A typical serum mucoprotein response to myocardial infarction. Case J. R., a sixty-six year old white male. Diagnosis: recent myocardial infarction of the anterior wall. It will be noted that there was no correlation between serum mucoprotein and sedimentation rate (Wintrobe).

of serum mucoprotein offered a great deal more information than the absolute serum mucoprotein level obtained at any specific time after the onset of the patient's attack. A definite elevation of the serum mucoprotein did not take place in all patients until the third day after onset of the attack. In individual cases there may or may not be an increase in this substance during the On the whole, this elevation was maintained until the ninth day; thereafter the serum mucoprotein concentration gradually declined, approaching normal values at the end of a month. After two or three months the values always returned to the normal range. In individual cases there was a variation in the time at which the mucoprotein level returned to normal. This may

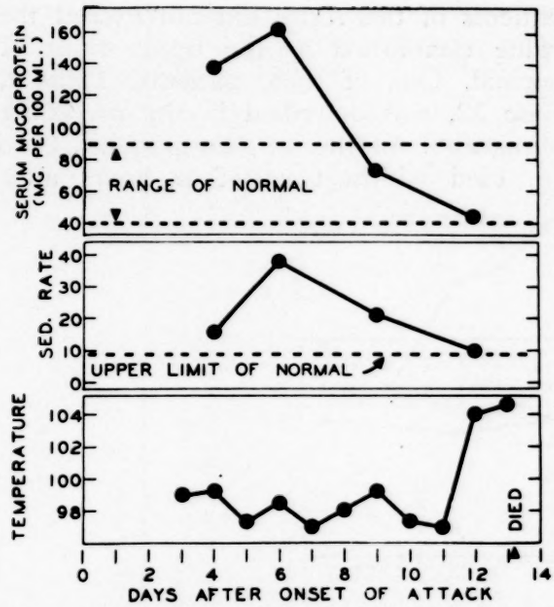

FIG. 3. Serum mucoprotein response to myocardial infarction with terminal azotemia and shock. Case L. M., a fifty-four year old white male. Diagnosis: recent myocardial infarction of posterior wall. The patient died with terminal azotemia and shock on the thirteenth day after coronary occlusion; no autopsy was obtained. A return to normal mucoprotein values occurred despite shock and terminal azotemia. In this case the sedimentation rate (Wintrobe) paralleled the serum mucoprotein values.

occur as early as the tenth day. Typical mucoprotein responses to myocardial infarction as shown in Figures 2, 3 and 4.

The following two cases illustrate the fact that serial mucoprotein determinations were more informative than any single level. In one, Table 1, Case 9, a patient who had bronchogenic carcinoma with bone metastases developed an anterior wall myocardial infarction. The characteristic rise and fall of serum mucoprotein noted after a myocardial infarction was superimposed upon an already elevated mucoprotein level caused by the pre-existent bronchogenic carcinoma. Although a single determination for mucoprotein would have meant little in this case, serial determinations aided in showing the characteristic changes observed following myocardial infarction. In the second case, Table 1, Case 22 (Fig. 5), a patient who had a coronary occlusion some months previously continued to have anginal attacks and was hospitalized because of severe substernal pain of two hours' duration. Serial determinations showed no change in the serum mucoprotein level

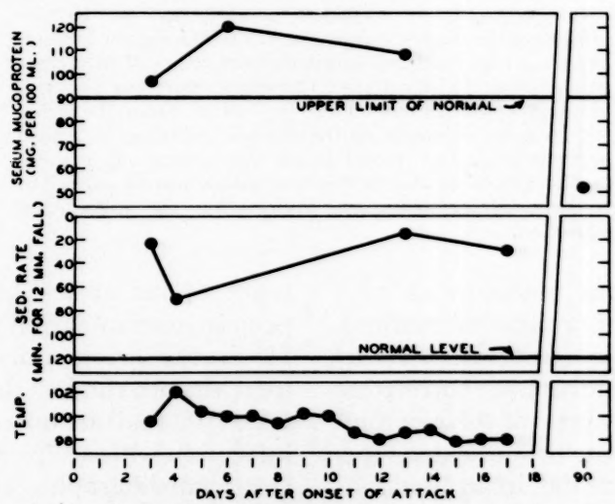
SERUM MUCOPROTEIN (MG. PER 100 ML.)
UPPER LIMIT OF NORMAL
SED. RATE (MIN. FOR 12 MM. FALL)
NORMAL LEVEL
TEMP.
DAYS AFTER ONSET OF ATTACK

FIG. 4. Graph illustrating optimum times for serial serum mucoprotein determinations. Case I. C., a sixty year old white male. Diagnosis: recent myocardial infarction of posterior wall. In this case the rise in serum mucoprotein during the first week aided in the diagnosis because the electrocardiographic changes were not well defined until the twelfth day. There seemed to be no apparent correlation between sedimentation rate (Linzenmeier) and serum mucoprotein.

which was below the usual range of normal. On the eighth hospital day he had another attack of severe substernal pain with collapse. Following this there was a rise of 22 mg. per 100 ml. in the concentration of serum mucoprotein. Although the highest patients of this series did not exceed the value established as the upper limit of normal. One of these patients, Table 1, Case 22, was described in the preceding paragraph. Another of these patients, Case 16, died within twenty-four hours after

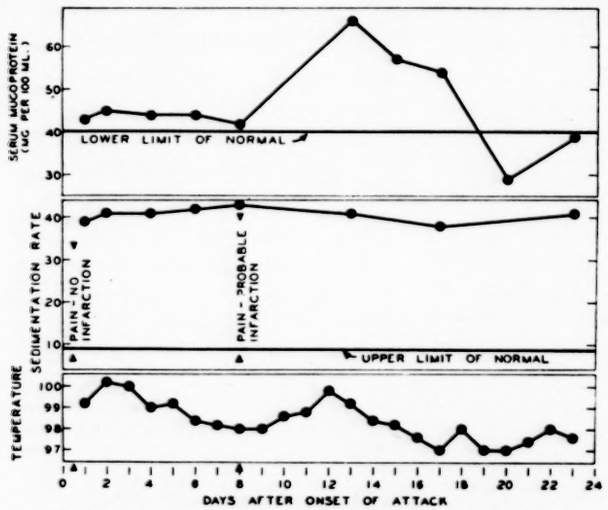

FIG. 5. Graph illustrating the importance of serial serum mucoprotein determinations although values occur within the normal range. Case I. S., a forty-nine year old male. Diagnosis: myocardial infarction. A patient with two previous coronary occlusions had angina pectoris for six months. He was admitted to the hospital with severe substernal pain. Despite fever and rapid sedimentation rate (Wintrobe) the serum mucoprotein remained normal and no electrocardiographic changes were noted. On the eighth hospital day the patient suffered another severe attack of substernal pain associated with collapse. The temperature was elevated, serum mucoprotein rose 22 mg. per 100 ml. above the previous level and changes in the electrocardiographic record were atypical. The second attack was interpreted as myocardial infarction whereas the first episode was considered to be premonitory symptoms anticipating the myocardial infarction.

absolute value of serum mucoprotein obtained was within the range of normal (66 mg. per 100 ml.), the significant increase in mucoprotein concentration, correlated with the characteristic curve of the rise and fall of serum mucoprotein, indicated the occurrence of a myocardial infarction following the second attack of pain. The occurrence of a few atypical ECG changes following the second bout of pain but not following the first strengthened this conclusion.

As just mentioned the highest mucoprotein level obtained in three of the onset of his attack and the single mucoprotein determination obtained was normal. However, serum mucoprotein may not be increased on the first day. The third patient, Case 10, had an anterior wall myocardial infarction with a typical clinical picture and electrocardiographic changes. In this case the mucoprotein concentration rose only 15 mg. per 100 ml. to a peak value of 93 mg. per 100 ml. Although a rise in serum mucoprotein did occur in this case, the findings were not considered clearcut enough to indicate a positive response to myocardial infarction.

TABLE 1

RELATION OF MYOCARDIAL INFARCTION TO SERUM MUCOPROTEIN

Case	Age	Sex	Diagnosis	Days after Onset of Attack Serum Mucoprotein (mg. per 100 ml.)																												
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	24	25	26	29	40	60	90	120
1 B	59	M	Old anterior wall infarct; recent posterior wall infarct						300							165						139						178		X*			
2 K	63	M	Anterior wall infarct										178						84					64								
3 S	61	M	Anterior wall infarct										151							122						116						
4 S	54	M	Posterior wall infarct						143							148																51
5 G	57	M	Posterior wall infarct					183									106															
6 H	33	M	Anterior wall infarct							136								74														
7 M	54	M	Posterior wall infarct; terminal azotemia; shock				101		143			64			35	X*																
8 B	40	M	Posterior wall infarct; gastrointestinal hemorrhage, cause unknown		72			103				102			115																	
9 C	63	M	Anterior wall infarct; bronchogenic carcinoma				195				216				200								181									
10 E	61	F	Anterior wall infarct				78				84				93							84										
11 H	70	F	Posterior wall infarct				148	X*																								
12 C	72	F	Anterior wall infarct					153			169	X*																				
13 G	35	M	Posterior wall infarct					105		104				99									92								70	
14 B	52	M	Myocardial infarct			112	X*																									
15 Z	53	M	Anterior wall infarct	100	118	X*																										
16 G	60	M	Lateral wall infarct	70	X*																											
17 R	66	M	Anterior wall infarct		98		117			118					119			113						97		91		88				
18 H	56	M	Posterior wall infarct	114	111	122	X*																									
19 W	63	M	Posterior wall infarct			91			118																							
20 C	60	M	Posterior wall infarct			97			120							108															47	
21 K	63	M	Posterior wall infarct												155						111						93					
22 S	49	M	Myocardial infarct, atypical	42				66		57		54			29			39														
23 L	54	M	Myocardial infarct							105			91																			

* X = expired.

In this series one patient, who entered the hospital with acute anterior wall myocardial infarction, was of unusual interest because he had another myocardial infarction on the twelfth hospital day. This was confirmed later at autopsy. In this case of these patients had developed a myocardial infarction. Two patients with paroxysmal tachycardia had normal serum mucoprotein values despite the findings of a rapid sedimentation rate in both. One patient with chest pain due to neuro-

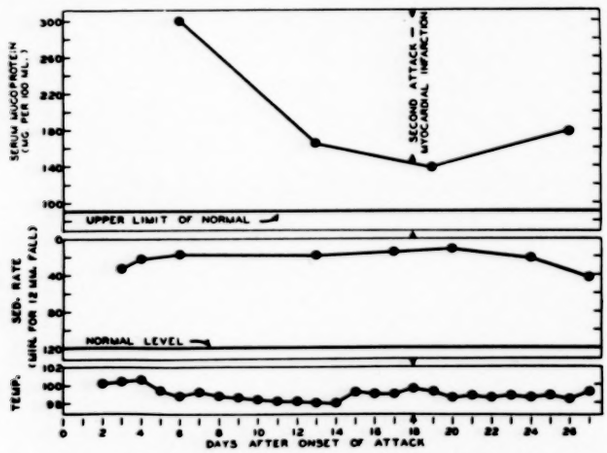
SERUM MUCOPROTEIN (MG PER 100 ML.)
SECOND ATTACK — MYOCARDIAL INFARCTION
UPPER LIMIT OF NORMAL
SED. RATE (MM. FOR 1ST HR. FALL)
NORMAL LEVEL
TEMP.
DAYS AFTER ONSET OF ATTACK

FIG. 6. Graph illustrating serum mucoprotein values following two myocardial infarctions. M. B., a fifty-nine year old white male, was admitted to the hospital with recent myocardial infarction of the anterior wall. Serum mucoprotein which was greatly elevated on admission was returning toward normal when the patient had a second attack of chest pain on the eighteenth day. Serum mucoprotein rose again and the electrocardiographic changes were indicative of a new posterior wall infarction. The patient died on the fortieth day after the initial attack. At autopsy an older anterior wall infarction and a recent posterior wall infarction were found. Again, no correlation between the serum mucoprotein and sedimentation rate (Linzenmeier) was found.

there was a marked rise in serum mucoprotein following the occurrence of each infarct. This is illustrated in Figure 6.

Serum Mucoprotein in Other Conditions Characterized by Chest Pain. Serial serum mucoprotein determinations were obtained in twelve patients who had prolonged attacks of chest pain due to causes other than myocardial infarction. Eight patients had angina pectoris or possibly myocardial ischemia without necrosis. In five of these patients serum mucoprotein determinations were performed after the occurrence of chest pain which was much more prolonged than usual. In all cases the serum mucoprotein levels were normal and did not change on subsequent determinations. Subsequent electrocardiographic and clinical findings failed to provide evidence that any circulatory asthenia showed no elevation of serum mucoprotein as did one patient with hypertension and chest pain on the basis of fibrositis. These cases show that serum mucoprotein values are normal and remain normal in patients with chest pain due to causes other than myocardial infarction or conditions not characterized by tissue destruction.

Serum Mucoprotein Findings in Miscellaneous Conditions. In addition to serum mucoprotein determinations in a control group of normal individuals, hospitalized patients with a variety of diseases were selected at random and tested. Normal serum mucoprotein values were found in patients with such diseases as hyperthyroidism, peptic ulcer, chronic brucellosis, splenomegaly of unknown etiology, temporal arteritis, ure-

mia, cerebral thrombosis, obstructive jaundice and urinary tract infection. Elevated serum levels were found in two cases of pneumonia, in three postoperative patients and in one case of bronchogenic carcinoma. Winzler in concurrent studies[3] found increased serum concentrations of mucoprotein in patients with pneumonia and with cancers. Abnormally low values for serum mucoprotein were found in a few patients with portal cirrhosis and infectious hepatitis and in one pregnant woman.

Relationship of Serum Mucoprotein to the Sedimentation Rate. In this study no constant relationship between the sedimentation rate and serum mucoprotein concentration was discernible. In patients with myocardial infarction acceleration of the sedimentation rate generally persisted longer than the elevation of serum mucoprotein. Figures 2, 4 and 5 illustrate cases of myocardial infarction in which there was absolutely no relationship between the serum mucoprotein concentration and the sedimentation rate. In a few cases of myocardial infarction there was a parallelism in the observed changes in the serum mucoprotein and the sedimentation rate. An example of this is shown in Figure 3.

In the group of twelve patients with chest pain due to causes other than myocardial infarction four patients exhibited accelerated sedimentation rates although in each of these patients the serum mucoprotein concentration was normal. Two of these patients had angina pectoris and two had paroxysmal tachycardia. Again it is apparent that no relationship exists between the sedimentation rate and serum mucoprotein level.

In Vitro Studies of Effect of Mucoprotein on Sedimentation Rate. Since it was possible that increased concentrations of serum mucoprotein could contribute to acceleration of the sedimentation rate, *in vitro* experiments were conducted to determine the effect of this mucoprotein component on the sedimentation rate. Known amounts of this mucoprotein material obtained from pooled human plasma* were added to blood withdrawn from each of three normal individuals. Aliquots of the blood obtained from each person were prepared to contain varying concentrations of mucoprotein ranging from 50 to 850 mg. per 100 ml. blood. A Wintrobe sedimentation rate determination was made with each of these blood samples. The results are shown in Table II. It was found that blood mucoprotein concentrations less than 150 mg. per 100 ml. had no effect on the sedimentation rate. In concentrations between 150 and 250 mg. per 100 ml. the mucoprotein material exerted a minimal effect upon acceleration of the sedimentation rate, and concentrations above 400 mg. per 100 ml. had a pronounced accelerating effect on the sedimentation rate. These findings were valid for both the uncorrected and corrected sedimentation rates.

TABLE II
EFFECT OF ADDED MUCOPROTEIN ON SEDIMENTATION RATE

Subject	Serum Mucoprotein (mg. per 100 ml.)	Mg. Mucoprotein Added per 100 ml. Whole Blood					
			0	100	200	400	800
C. R. (M)	56	ESR*	20	25	24	32	42
		PCV†	48	48	48	43	41
		CSR‡	20	26	25	26	32
H. B. (M)	47	ESR	22	20	26	29	39
		PCV	46	47	45	44	41
		CSR	21	20	23	25	32
E. F. (F)	63	ESR	18	19	23	29	43
		PCV	42	42	42	39	36
		CSR	18	19	23	24	32

* Estimated sedimentation rate.
† Packed cell volume, per cent.
‡ Corrected sedimentation rate (Wintrobe).

These results show that the sedimentation rate is not affected to any appreciable extent by the increased concentrations of mucoprotein usually found in the serum following myocardial infarction. The acceleration of the sedimentation rate often noted in this

* A sample of lyophilized mucoprotein obtained from pooled human plasma was provided through the kindness of Dr. Richard Winzler.

condition is undoubtedly caused by chemical changes in the blood other than that reported here.

COMMENTS

The nature of the metabolic changes occurring in patients with myocardial infarction has received little study. Recently Altschule et al.[6] reported several observations on metabolic changes in patients with myocardial infarction. Their findings, in addition to our own reported in this communication, suggest the desirability of further biochemical studies in patients with myocardial infarction.

On the basis of the preliminary studies presented herein the increase in the concentration of serum mucoprotein following myocardial infarction appears to be a fairly regular phenomenon and one which at times may be useful as an aid in establishing the diagnosis of recent myocardial infarction. Moreover, this procedure has also proved helpful in ruling out the occurrence of myocardial infarction following a bout of chest pain. No increase in serum mucoprotein was observed in patients with chest pain due to angina pectoris, paroxysmal tachycardia, neurocirculatory asthenia and fibrositis. Increases were found, however, accompanying chest pain associated with bronchogenic carcinoma and pneumonia.

In the small number of cases studied thus far the serum mucoprotein findings appeared to correlate more closely with the presence or absence of myocardial infarction than the sedimentation rate. In several cases rapid sedimentation rates were obtained in patients with angina or paroxysmal tachycardia, but the serum mucoprotein concentration remained unchanged. Conversely, one patient with fresh anterior wall myocardial infarction did not exhibit a rapid sedimentation rate until the seventh day after the onset of illness although his serum mucoprotein level was elevated on the second day. Examination of some of the graphs of individual patients shows that the serum mucoprotein values and sedimentation rates were independent of each other although in several instances they paralleled each other.

In vitro experiments on the relationship of the mucoprotein material to the sedimentation rate showed that serum mucoprotein in concentrations usually found after a myocardial infarction had little or no influence on the acceleration of the sedimentation rate. A marked accelerating effect on the sedimentation rate does not occur until concentrations are reached which are far beyond the usual elevated pathologic values. The explanation for the effect of very high concentrations of the mucoprotein component on the sedimentation rate may be that because this material is a macromolecular substance (molecular weight approximately 50,000) it, like other macromolecular substances, accelerates the sedimentation rate.[7,8]

Since this mucoprotein component has little or no influence on the sedimentation rate, an investigation of the changes in the protein components of the serum following myocardial infarction would be of great interest. In this connection Shedlovsky and Scudder[9] have reported the electrophoretic findings in two cases of myocardial infarction at one week and at six weeks after the onset of infarction. They found increases in the alpha globulin fraction.

When this study was begun, it was hoped that a substance specific for the breakdown of infarcted heart muscle could be found in the blood or urine. Serum mucoprotein is *not* a specific product of the death of cardiac muscle alone. Increases in the serum mucoprotein have been found in other conditions. For example, in this laboratory elevated serum mucoprotein levels were also obtained in postoperative patients and in patients with cancer and pneumonia. Earlier workers[10] have reported unusually high polypeptide* concentrations in the

* The chemical methods employed by previous workers to measure serum polypeptide or proteose concentrations are similar in principle to the method employed in this study; hence, it is possible that the determinations of serum polypeptide, proteose and mucoprotein by the various authors are all determinations of essentially the same serum protein constituent.

blood as a result of acute hepatic insufficiency, burns, trauma and cancer. Excretion of proteoses in the urine has been described in various allergic states.[11,12] Winzler and Burk confirmed and extended the observations of earlier workers who found elevated serum proteose* levels in patients and animals with cancer. In studies on the rat they also found increased serum proteose levels in acute and chronic infections such as pneumonia, chronic cecitis, in advanced pregnancy and as a consequence of severe tissue injury or shock. Selye[13] mentions the increase in blood polypeptides as one of the changes found in the "alarm reaction." All of these observations certainly point to the fact that the elevation of serum mucoprotein is a non-specific phenomenon which is the result of a variety of causes. However, there appears to be one common denominator present in every condition characterized by an increase in serum mucoprotein: a breakdown of tissue proteins. Selye emphasizes this viewpoint when he states that "the extensive protein breakdown characteristic of the shock phase of the alarm reaction is probably the cause of the increase in polypeptides."

Although this study was undertaken with the view that serum mucoprotein was derived from the breakdown of tissue proteins, there is no direct proof as yet that this is true and there are other theories[14–16] concerning the origin of this material: (1) failure of the liver to metabolize the normal amounts of mucoprotein formed, (2) failure of the kidney to excrete them normally and (3) degradation of plasma proteins. It is unlikely that a failure in liver function can account for the elevation in serum mucoprotein found in these and other studies because we have found very low serum mucoprotein values in patients with acute infectious hepatitis or with advanced Laennec's cirrhosis. It is believed that renal insufficiency is not a factor in the elevation of serum mucoprotein inasmuch as we have obtained normal values in two patients in the terminal phase of uremia. At present studies to determine the origin of serum mucoprotein are being conducted by Winzler.[2]

Further studies on the detection of other breakdown products of infarcted heart muscle which may be more specific are contemplated in this laboratory. At the present time this appears to be a fruitful field of endeavor.

* See footnote on page 742.

SUMMARY AND CONCLUSIONS

1. In twenty-three patients with recent myocardial infarction, serum mucoprotein values were consistently found to exceed the normal range of 40 to 90 mg. per 100 ml. The actual rise above each patient's presumed normal value varied from 22 to 160 mg. per 100 ml.

2. A characteristic rise and fall of serum mucoprotein followed the clinical onset of symptoms. Serum mucoprotein was definitely elevated by the third day after clinical indications of coronary occlusion with myocardial infarction were evident. The peak of the rise occurred on the sixth day and this elevation was usually maintained for another week after which the serum mucoprotein gradually declined and approached normal values at the end of a month.

3. Serum mucoprotein values in patients with chest pain due to causes other than myocardial infarction were within the normal range in cases including angina pectoris, paroxysmal tachycardia, neurocirculatory asthenia, hypertension and fibrositis. No increase was found by single or serial determinations.

4. In the present study no consistent relation was found between the sedimentation rate and serum mucoprotein. In general, accelerated sedimentation rates persisted longer than elevated serum mucoprotein following myocardial infarction. In several patients with angina pectoris and paroxysmal tachycardia the sedimentation rate was increased whereas the serum mucoprotein was normal.

5. *In vitro* studies on the effect of added mucoprotein upon the sedimentation rate

of normal blood showed no marked acceleration until a concentration of proteose exceeding 400 mg. per 100 ml. was obtained, concentrations beyond the usual values in myocardial infarction. It is obvious then that other factors are responsible for development of the rapid sedimentation rate observed in myocardial infarction and that serum mucoprotein is not another measure of the sedimentation rate.

6. In the cases reported in this study the increase in serum mucoprotein appeared to reflect more accurately than the sedimentation rate or leukocyte count the presence or absence of myocardial necrosis.

7. Although serum mucoprotein changes following myocardial infarction are not specific for this condition alone, determination of serum mucoprotein may be useful as a diagnostic aid in evaluation of clinical syndromes caused by coronary artery disease.

Acknowledgment. We are indebted to Dr. Richard Winzler for his valuable advice and cooperation in the performance of this study.

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Clinical Value of Serum Polysaccharide Determinations by the Tryptophane-Perchloric Acid Reaction*

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ALTHOUGH normal human serum is known to have a polysaccharide content equal to or greater than its glucose content, the polysaccharides, which are measured with difficulty, have not been completely identified. The polysaccharide concentrations in pathologic sera have been studied in a few instances in the past and elevated values were reported in patients with carcinoma,[1] pneumonia[2] and other infections.[3]

Renewed interest in this subject has recently been stimulated by investigations in diverse fields. Seibert's electrophoretic studies[4] in tuberculosis, Winzler's polarigraphic studies[5] in carcinoma and Meyer's studies[6] of hyaluronic acid have led these investigators to the study of glycoproteins and their carbohydrate components.

The total polysaccharide of normal human serum has been found by Shetlar, Foster and Everett[7] and by Seibert[8] to range from 80 to 130 mg. per cent. Seibert[9] has reported elevated polysaccharide levels in the sera of patients with advanced active tuberculosis and with carcinoma. Winzler,[10] studying mucoprotein concentrations, reported increased serum levels in patients with carcinoma and pneumonia while Prinzmetal et al.[11] found the concentration of proteoses (containing 25 per cent carbohydrate) increased in patients with acute myocardial infarction.

In an attempt to distinguish the polysaccharides derived from a breakdown of nucleoproteins, which might more specifically reflect tissue destruction, Seibert[12] adapted for use on serum the tryptophane-perchloric acid reaction which Cohen[13] had developed for detection of the carbohydrate of desoxyribonucleic acid. This test, which is simple enough for routine use in clinical laboratories, gave both in experimental rabbit tuberculosis[14] and in patients with tuberculosis, results which showed a highly significant correlation with extent and activity of the disease. Although the identity of the polysaccharides measured by the tryptophane-perchloric acid reaction remains uncertain, Seibert's observations on the clinical value of application of this test in tuberculosis led to the present attempt to determine its value on a general hospital service. A survey of representative patients has been made and the results of tryptophane-perchloric acid tests have been correlated with clinical, pathologic and other laboratory findings, with special interest in ascertaining whether serum polysaccharide determinations provided information of clinical value greater than that obtainable with the sedimentation rate and with routine serum protein studies.

MATERIAL AND METHODS

Determinations were made on 102 specimens from ninety patients and six healthy controls. Patients were selected from the wards of the Woman's Medical College Hospital, the Philadelphia General Hos-

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pital and the Philadelphia Hospital for Contagious Diseases in an attempt to encompass a variety of disorders. Samples of blood (6 to 8 cc.) were obtained, not under fasting conditions, centrifuged and the serum obtained and placed in a deep freeze unit. Ten sera, each in triplicate, were run at one time according to Seibert's modification[12] of Cohen's method. The mean of the three values was recorded as the final result. Because of doubt as to the nature of the polysaccharides measured, conversion to more specific terms has not been attempted and results are expressed in Klett units, as suggested by Seibert.

Simultaneous oxalated specimens of blood were obtained for sedimentation rate determinations by the Wintrobe method, which were performed within three hours of collection. Correction for anemia was not made. Serum albumin and globulin determinations were performed by the clinical laboratories of the hospitals, employing the method of Kingsley.[15]

RESULTS

A group of six healthy controls gave polysaccharide levels by the tryptophane-perchloric acid reaction ranging from 41 to 57 Klett units with a mean of 47.3 ± 6.2 units. (Table 1.) Seibert[12] found among thirty normal persons a range from 32 to 79 units with a mean of 60 ± 12.9 units. Combining these control groups gives a mean of 58 ± 12.4 Klett units. Values within two standard deviations of this mean, that is values less than 83 units, have been considered in this study to fall within the normal range.

TABLE 1

SERUM POLYSACCHARIDES, SEDIMENTATION RATES AND SERUM PROTEINS

Diagnosis	No. of Patients	Serum Polysaccharides (Klett units) (mean)	Sedimentation Rate (mean)	Serum Albumin (mean)	Serum Globulin (mean)
Neoplasms	10	103.5 ± 32.3	51.0 ± 5.5	3.6 ± 1.4	3.1 ± 1.1
Chronic infections	14	103.5 ± 26.8	33.6 ± 23.7	4.1 ± 1.8	2.3 ± 0.7
Hyperthyroidism	4	97.2 ± 15.8	45.0 ± 14.8	4.3 ± 2.2	2.2 ± 0.4
Cardiovascular disease	14	92.2 ± 23.2	35.7 ± 18.5	3.8 ± 1.6	2.6 ± 0.7
Rheumatic fever	5	80.0 ± 18.2	31.0 ± 26.8	4.9 ± 2.1	2.7 ± 0.5
Hepatic disease	7	79.6 ± 26.6	44.7 ± 9.5	3.3 ± 1.2	3.2 ± 0.3
Acute infections	15	79.0 ± 22.7	39.4 ± 18.7	4.0 ± 1.5	2.5 ± 0.4
Miscellaneous disorders	14	77.0 ± 16.2	35.0 ± 17.4	3.9 ± 1.9	2.2 ± 0.3
Pregnancy	7	64.6 ± 10.6	49.0 ± 5.0		
Normal subjects	6	47.3 ± 6.2	13.1 ± 5.6		

In a group of seven obstetric patients, three antepartum and four immediately postpartum, six had values ranging from 55 to 70; the seventh had a level of 87 Klett units. In all of the obstetric patients the sedimentation rate was extremely rapid. Among the eighty-three patients with a variety of diseases of varying severity fifty-one had levels of 83 Klett units or more and thirty-three had levels below this value. High values were obtained (Table 1) in patients with chronic infections, neoplasms, hyperthyroidism and cardiovascular disease. Less marked elevation was noted in patients with rheumatic fever, hepatic disease, acute infections and in a miscellaneous group including patients with gastrointestinal, hematologic, genito-urinary and dermatologic disorders.

Figure 1 indicates the lack of significant correlation between the serum polysaccharide levels and the sedimentation rate determinations. Similar analyses show absence of correlation between the polysaccharide levels and serum albumin, serum

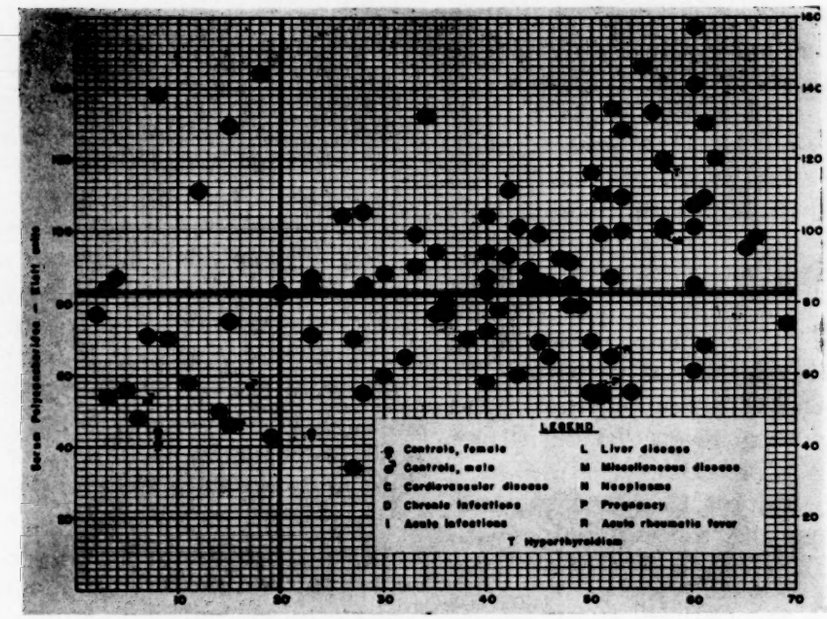

FIG. 1. Serum polysaccharides and the sedimentation rate (Wintrobe), mm. per hour uncorrected.

globulin and hemoglobin concentrations and leukocyte counts.

Neoplasms. Ten patients with histologic diagnoses of neoplasm were studied, three patients with carcinoma of the gastrointestinal tract, one of the bladder, one of the cervix and one of the larynx, as well as three patients with lymphoblastoma and one with neurofibroblastoma. Seven showed elevated polysaccharide values with the highest values, 141, 146 and 157, in the patients with gastrointestinal carcinoma. Three patients, two with carcinoma and one with lymphoblastoma, had values below 70. Sedimentation rates were rapid in all instances except in the patient with lymphoblastoma and with normal polysaccharide level. Serum protein studies revealed in most patients of this group depressed albumin levels and increased globulin levels. No correlation between these changes and those in polysaccharide content was noted.

Chronic Infections. Abnormal Klett values ranging from 84 to 144 were observed in ten of fourteen patients with chronic infections. Patients with amebic hepatic abscess, chronic pulmonary abscess and meningovascular syphilis, respectively, had elevated polysaccharide levels with normal sedimentation rate. Patients with active minimal tuberculosis and rheumatoid arthritis had normal polysaccharide levels and an abnormal sedimentation rate. Patients with rheumatoid arthritis, pyelonephritis, bronchiectasis, lung abscess, meningovascular syphilis and ulcerative colitis had increased polysaccharides and abnormal sedimentation rates.

Hyperthyroidism. Three patients with diffuse hyperthyroidism and one with a toxic adenoma of the thyroid were studied. All had elevated polysaccharide levels, ranging from 83 to 121 Klett units, and in all instances the sedimentation rate was abnormally rapid and the serum protein fractions normal.

Cardiovascular Disease. Of fourteen patients with cardiovascular disease ten had elevated polysaccharide levels. The four patients with malignant hypertension and the three with acute myocardial infarctions showed elevated polysaccharide levels, as did patients with decompensated rheumatic heart disease and two patients with pulmonary infarction. Normal values were observed in patients with hypertensive heart disease, benign hypertension, inactive rheumatic heart disease and syphilitic

heart disease with congestive failure. In this group sedimentation rate findings tended to parallel those of the polysaccharides.

Rheumatic Fever. Five patients with clinically active rheumatic fever were studied. Moderate elevation of the polysaccharide level was noted in four of the five patients in this group.

Hepatic Disease. Two patients with cirrhosis and one with infectious hepatitis had polysaccharide levels ranging from 83 to 130 Klett units and three patients with cirrhosis and one with homologous serum hepatitis had normal levels. In this group there was a notable lack of correlation between sedimentation rate and polysaccharide findings: the three patients with low polysaccharide levels had rapid sedimentation rates. Four of the five patients with cirrhosis had a characteristic increase in globulin and decrease in albumin concentration.

Acute Infections. Elevated polysaccharide levels were found in only eight of fifteen patients with acute infections. Patients with meningococcic meningitis. Streptococcus viridans endocarditis under treatment, hemolytic influenzae pneumonia, mumps and rubeola showed normal levels ranging from 48 to 74, while patients with pneumococcal pneumonia and meningitis, scarlet fever, rubeola, Friedländer's pneumonia and typhoid fever showed values ranging from 89 to 115. In this group the sedimentation rate was usually increased out of proportion to the polysaccharide elevation; in no instance in this group of patients was the sedimentation rate normal in the presence of abnormal polysaccharide levels.

Miscellaneous Diseases. In this group, which includes patients with hematologic, gastrointestinal, genito-urinary and dermatologic disorders as well as several instances of minor illnesses in which a definite diagnosis was not established, elevation of the polysaccharides was infrequent: only five of fourteen patients had abnormal values. Six of the nine patients with low polysaccharide levels had elevated sedimentation rates.

COMMENTS

Although the tryptophane-perchloric acid reaction was employed by Seibert originally to detect desoxyribonucleic acid, subsequent investigation revealed that the carbohydrate measured by this test in normal and pathologic sera was not a single substance. Detailed analysis[12] suggested that the polysaccharide measured might be a mixture of desoxyribonucleic and ribonucleic acids and their derivatives, a fructose complex, or even a carbohydrate-protein complex similar to the mucoprotein under investigation by Winzler. An important advantage of this test over those used for determination of total serum polysaccharide content is its ease of performance which permits its use as a routine procedure in general hospital laboratories. Seibert[1,12] found elevated polysaccharide concentrations to be correlated with increases of alpha-2 globulin in the sera of patients with tuberculosis and carcinoma. Whether the increased polysaccharides observed in the sera of patients in this study with neoplasms, chronic infections, hyperthyroidism and cardiovascular disease are related to increases in alpha-2 globulin is not known, since electrophoretic analyses were not available. No correlation was observed between the polysaccharide content of sera and the albumin and globulin concentrations as measured by ordinary clinical laboratory methods.

Special interest exists in comparison of the tryptophane-perchloric acid reaction with the sedimentation rate, which has found a wide field of usefulness because of its simplicity. The sedimentation rate has become firmly established as a valuable aid in the study of arthritis, tuberculosis and in general medicine, even though the mechanism underlying acceleration of erythrocyte sedimentation is not definitely known. Gutman[16] has recently reviewed the conflicting evidence concerning the relation of sedimentation and serum protein alterations and has concluded that an increase in fibrinogen content of serum plays a major role and increases in alpha,

beta and gamma globulins play a lesser role in accelerating sedimentation of erythrocytes; a decrease in serum albumin enhances the rate of sedimentation. Meyer[17] has suggested that accelerated sedimentation may be due to increased amounts of glycoproteins in the serum and has demonstrated that the addition to serum of hyaluronic acid, a mucopolysaccharide, markedly increases the rate of sedimentation. In the clinical material studied in the present investigation, however, sera with high polysaccharide content as shown by the tryptophane-perchloric acid reaction often did not exhibit rapid sedimentation rates. Conversely, patients with extremely rapid sedimentation rates, e.g., in pregnancy, frequently showed low polysaccharide levels. Gutman[16] has pointed out that different protein changes may be responsible for the rapid sedimentation rates of acute infections and those of chronic infections. The observations in the present report indicate that serum polysaccharide determinations may have clinical value in the differentiation of acute and chronic infections.

The sedimentation rate is of limited value in obstetric practice because rapid sedimentation is almost invariably present during pregnancy and the postpartum period; the serum polysaccharides are apparently rarely elevated in uncomplicated pregnancy and their determination may prove useful in the detection of intercurrent diseases.

The sedimentation rate is used frequently as a means of excluding serious disease. For this purpose the tryptophane-perchloric acid reaction appears to be a valuable corroborative test. Patients in the present study with normal sedimentation rates and normal serum polysaccharide levels rarely proved to have a serious disease.

SUMMARY

1. Seibert's modification of the tryptophane-perchloric acid reaction has been employed to determine serum polysaccharide levels in a survey of general hospital patients.

2. Elevation of the serum polysaccharides was most marked and frequent in patients with neoplasms, chronic infections, hyperthyroidism and cardiovascular diseases. Abnormal values were less often observed in patients with acute infections, hepatic disease, rheumatic fever and miscellaneous disorders. Normal values were the rule in pregnancy.

3. Serum polysaccharide elevation appears to reflect biochemical changes different from those measured by sedimentation rate and other routine laboratory studies.

Acknowledgments: The assistance of Florence B. Seibert, Ph. D., Associate Professor of Chemistry, Henry Phipps Institute of the University of Pennsylvania and her staff and that of Phyllis Bott, Ph. D., Professor of Physiological Chemistry, the Woman's Medical College, and her staff are gratefully acknowledged.

Financial aid from the Anonymous Fund of the Woman's Medical College is also gratefully acknowledged.

In addition thanks are due to the Research Committee of the Philadelphia Hospital for Contagious Diseases for permission to study patients with acute contagious diseases.

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What Can We Learn from a Medical History?*

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EXPERIENCE teaches most of us that time spent in obtaining a careful medical history is time well spent and will save wasted motions later. What we actually can learn will depend, of course, on our skill and on the patient's willingness and capacity to cooperate with us. Although I shall discuss both of these topics later, it will be more appropriate to consider first what we should aim at when taking a medical history.

Naturally this will depend on our purpose. As I understand it the purpose of taking a medical history is to record a series of events that have culminated in the illness or disorder for which the patient has consulted us. It is assumed that from such a record we shall get some understanding of the sick person and of his ailment and, furthermore, that others trained in medicine will derive a similar understanding from reading the history that we have written down.

No medical history, however, can reproduce accurately what occurs in nature. It is at best a kind of stylized symbolic representation of certain human experiences in much the same way that a map is a stylized symbolic representation of a landscape. The value of a good map will depend upon the accuracy of its scale and upon the picturing of the relationship of certain important land masses, contours, bodies of water, as well as certain man-made structures such as railroads and large settlements. With the aid of such a map, we can find our way around in strange country. But if the map depicts every culvert, duck pond and hot dog stand and leaves out mountain ranges and navigable rivers, we will soon go astray if we rely upon it. Just so a good medical history will portray in the dimension of time, rather than space, the influences, past and present, that are important in the development of the patient and his disorder. You may justifiably catch me up on the word *important*. There is no question about the importance of a mountain range or a navigable river but who is to say what is important in the record of a patient's life. If we depend wholly on his judgment, then of what use is our medical knowledge; and if we depend wholly on our own preconceived notions, then we will arrive at a kind of standardized history which includes everything and tells us nothing.

When I was an intern, we were taught to take just such histories. We would approach a patient and after recording his complaint (this we were taught to put down strictly in the patient's own words, an excellent habit to which I have always clung) we would write the letters, F. H., for family history. That was quickly disposed of with: The patient's F. was l. and w. but his M. had unfortunately d. of typhoid fever. A number of S's and B's were usually l. and w. or a couple might have d'd in infancy. And then the ritual was to say that the F. H. was otherwise "non-contributory" (a truly fabulous misconception!) and that there was no tuberculosis (later we added "or known exposure") or malignant disease in the family. We would then go on to the P. H. No illness or accident would escape us. We were as persistent as a cigar-smoking detective in a movie melo-

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drama and about as subtle. I recall asking a young woman about her weight. What was her present weight, her weight last year and her heaviest weight? When I asked her what her lightest weight was and she said "5½ pounds"! I began to get the notion that perhaps I was boring her by the third degree method.

I recall the chief attending physician, a sober and pedestrian man, asking a little boy of eight whether the pain in his groin radiated to his penis and testicles. The child looked up bewildered and said: "What's them"?

Then with a rumble of drums came the last and final act of the circus, the P. I. This was a new event, a thing in itself, a calamity, a misfortune, an act of God like a hurricane or an earthquake. It had little to do with past events and less with what today we call the personality. Our histories were nothing if not complete. They covered pages of carefully written foolscap. The greatest sin was the sin of omission. And they bore about as much resemblance to the true story of the patient's life as a Mercator projection does to the contours of the earth's surface.

During World War I I was for a time put in charge of a large medical ward in a Base Hospital in France. Although I was only a First Lieutenant, casual officers outranking me by several grades were assigned to this ward for instruction in physical diagnosis. One of them had the habit of turning in long and rambling medical histories that stretched out interminably and arrived nowhere. I urged this officer as tactfully as I could to stick to the essentials. The next history that he wrote up was a short one. It said:

> Complaint: Abdominal pain
> Past history: Kicked by a steer
> Diagnosis: Tonsillitis.

This has always seemed to me a paradigm of the nonsequitur and an excellent caricature of many medical histories today. For the method I have just been describing is by no means as quaint and antiquated as I have made it sound. It is the current method in most general hospitals and in many private offices although in some, history taking is but a scanty business or is turned over to an office nurse who at the same time sizes up the patient's probable income.

Perhaps in only a few places has psychiatry made its inroads on the medical curriculum and modified this traditional way of taking histories. This is psychiatry's greatest contribution to clinical medicine, the introduction of what I have called elsewhere, scientific biography.

There is no doubt that a new type of medical history is being developed although as yet it has not been formulated and in only a few medical schools, to my knowledge, is it being deliberately taught. If such a change is occurring, it is, as I have said, largely due to the influence of modern dynamic psychiatry. But there are other reasons as well that have contributed to it.

The establishment of the germ theory of disease in the latter part of the last century set the pattern for much of the investigative work of the following half century. Koch's laws became the Magna Charta of medical research. To isolate a germ and to prove its specific pathogenicity, this was the greatest scientific achievement. And why not? When one considers the triumphs and blessings that have resulted from such studies, it was natural that this type of thinking should have dominated clinical medicine and that in large measure it still does. The successes that were achieved have, as is well known, reduced the incidence of infectious diseases and brought into relative prominence the degenerative diseases and stress reactions. To these conditions such simple unitary etiologic thinking, as exemplified by Koch's laws, seems far less applicable. We are no longer dealing with such invariable relationships as might be expressed in the statement: A acting on B produces C. Illness is not always the immutable effect of some one cause but rather the outcome of a process of development in which innumerable factors play a role. We have had to develop new theories and concepts of disease and also new methods of study.

Our aim in taking a medical history is no longer simply to find an etiologic agent and then to devise means of exorcising it. It is rather to discover what kind of individual we are dealing with, what are his strengths and weaknesses, his assets and liabilities, what his patterned reactions are under stress and in what respects do the bodily defenses, which he mobilizes, themselves turn into malign and damaging forces?

Harold Wolff[1] has put this well when he says that although man's protective activities may be life-saving if they are used in emergencies to destroy the forces that threaten him, the same protective activities when used as life-long patterns may damage the very structures they were devised to protect.

Perhaps Shakespeare had a similar principle in mind when he had Hamlet say:

"Find out the cause of this effect,
Or rather say, the cause of this defect,
For this effect defective comes by cause."

Since in the modern world we are constantly being confronted by new and changing environmental situations and since the human organism has only a limited number of ways in which it can respond to these changes, it is clear that much of clinical medicine will be concerned with the problem of homeostasis. How does the organism strive to maintain a steady state, both psychologically and physiologically? Are its efforts effective and efficient? This is the general line of inquiry that a modern medical history must pursue. To do so the form of the history has to be greatly revised. We pretty much have had to give up the question and answer game which some years ago led us so securely, at least so we thought, to our goal.

A wise physician today will recognize that in a great many instances he cannot possibly know just what questions to ask and, furthermore, even if he did, the patient could not answer them. Obtaining a medical history has become primarily a personal voyage of discovery into unknown territory. Physician and patient are joined in a common enterprise to uncover certain facts. Often the patient is a laggard and will resist progress and as often the physician, because of his own emotional blindness, will not be able to see or understand what is before him.

This is true of a medical history as well as of a psychiatric one. In my opinion there is not much difference between them except that imposed by time and by the emphasis of the immediate complaint. Since the medical history has become, or should become, more fluid and more elastic at once, no form or syllabus will really suffice, no printed list of queries against which one places check marks. These may have their value when one is engaged in a specific research project and is trying to get answers to certain set questions. Or again, printed forms may have their uses in dealing with large numbers of patients when saving of time and medical personnel is of moment. But, important as they may be, I am not concerned with them now but rather with how this new method of history taking can be described, formulated and taught.

Let us begin at the beginning. In spite of all our protestations about "the patient as a person" the young medical student still looks upon him as a case of this or that. If he does, it is our fault because we still believe in a kind of Platonic abstraction called disease as if it existed outside the body of the sufferer. The conventional and jejune introduction to most medical histories states that: "The patient is a white male sitting comfortably in bed." The student seldom knows the patient's name and if he does the national origin of the name means little to him. Actually it makes a great deal of difference whether the patient is called Mr. Feitelbaum, Mr. Finnegan or Mr. Ford. As I look over some of my own records I find such unconventional statements as Miss Smith looks like "a languid lily," "Mr. Jones looks like a snapping turtle with a gold watch chain," or again, "Mr. T. is an artist of Finnish origin but with a Yankee accent. He looks like a pink-cheeked beer barrel." You may

protest that these are unscientific statements, that they introduce a subjective element which colors the material. But do not be deceived, it is quite impossible to keep out one's subjective judgments and opinions and it is no more scientifically accurate to describe the patient as though he were a puppet or a manikin.

It would be a great benefit to medical students if we could teach them the art of history taking in medical out-patient departments and not on the wards. A bank teller or the corner grocer's wife cease to be themselves when we rob them of their usual plumage and put them into hospital night clothes. Furthermore, they are different people when sitting opposite us in a chair from what they are when "lying comfortably" in a hospital bed. The very fact that a hospital bed is so strangely tidy and high from the ground makes them different from what they would be in their own birds-eye maple or golden oak Grand Rapids variety.

What the student should see as clearly as he can, is the patient's *persona*, i.e., what front does he present to the world? If he knows the patient's name and calls him by name, he will naturally get a more accurate picture of him because the patient will respond in a less guarded way. The student should then shake hands with the patient. This is not only a civil thing to do but much can be learned from a handshake. Does the patient present the tips of his fingers only in an uncertain and limp way? Is he a bone crusher? Are the hands wet, cold and tremulous? Does the handgrasp cling lovingly as it does in many alcoholics? Or cannot the patient release his grasp as was true of a patient I saw who was afflicted with muscular dystrophy with pronounced weakness of the extensor muscles?

Having established this contact, the student should be taught to exhibit some interest in the patient's welfare. It does not make much sense to approach a sufferer with a gastric ulcer and ask him right off the bat whether he was a breast baby or a bottle baby even if this fact is important to ascertain. The patient should be encouraged to talk about the here and now, about what ails him. Why has he come to the hospital or come to consult the physician? Many present day patients think that they are helping us most by giving a kind of prepared historical review of their lives, beginning with their parents unhappy marriage and how they were jealous of their younger sisters. A colored cook recently said to me: "I have a terrible pain in the back but I know it's all due to my inferiority complex."

The physician must go along with such comments but gradually lead his patient to talk about what ails him. It is far better to proceed from the present backward although in the final write-up the history may be presented in reverse order. We must pay strict attention to how the patient behaves during the interview, to the language he uses, to his attitude toward his symptoms and to the anxiety with which they are associated. We must keep our ears cocked for what has been called "body language." What is the body trying to say that the patient cannot say?

During the course of such an examination we can include, without the patient's ever knowing it, some of the usual psychologic tests for memory, symbolization, logical faculty and general intelligence. We do not need to have the patient say "methodist episcopal" in order to spot a dysarthria. We must above all get some knowledge of prevailing moods and suppressed emotions which may express themselves physiologically.

As I said at the beginning what we are aiming at in taking a history is a knowledge of the person as well as of his illness because in most instances, perhaps in all, they are inextricably related. The method of what has been called "associative anamnesis"[2] is a useful one. The patient is encouraged to talk freely. We interrupt him to guide him into productive channels, not by interposing new questions but by picking up one of his own statements and modifying it just enough to rephrase it into a query that will serve as a new point of departure. From

the mass of material so obtained we try to reconstruct a life history. We draw a map to help us find our way, but we must never forget that the map making is a combined enterprise of patient and physician. It is for this reason, not for sentimental ones, that the physician-patient relationship is the basis both of history taking and of subsequent therapy.

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Review

Fluorocardiography (Electrokymography*)

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THE clinical importance of obtaining accurate records of volume changes and motions of the cardiac chambers and the large vessels is self-evident. Many clinical problems in the field of cardiology have been successfully studied by graphic methods such as cardiography, sphygmography, phlebography and esophagocardiography. However, these methods permit but indirect conclusions as to the heart action and are limited in their scope and accuracy. Roentgenologic visualization of the cardiovascular silhouette offered a new approach to more direct records. Roentgenocinematography would be a desirable method for this purpose but is too cumbersome and expensive for general use and has been supplanted by roentgenkymography,[1–9] a method screening out one or several points of the cardiac silhouette by a slitted diaphragm and moving a film in a direction perpendicular to the slits. The tracings so obtained record the movements of these particular points of the heart silhouette.

Roentgenkymography was received with great expectations but its physiologic and technical limitations were soon recognized. The inherent physiologic limitation is due largely to the fact that the visible motion of the heart is a composite of changes in volume and changes due to motion of the heart as a whole. Attempts have been made to overcome the technical limitations of roentgenkymography which consist of limited speed and recording time, lack of detail and distortion of the recorded waves. With the advent of light-sensitive electronic tubes, these served as immobile receptors for the moving x-ray films.

THE APPARATUS

The first apparatus of this kind for practical use was developed by Henny and Boone who called their method electrokymography (1945),[23] followed by Lian and Minot (radioelectrokymography, 1946),[20] Marchal (kinedensigraphy, 1946)[21] and Luisada, Fleischner and Rappaport (fluorocardiography, 1947).[31–33] These various apparatus and technics are based on a common principle although they are different in structural details, sensitivity and accuracy.

The arrangement used by Luisada, Fleischner and Rappaport[32] consists of: (1) fluoroscope; (2) pick-up device attached to a fluoroscopic screen made up of a photo-multiplier tube (RCA-931-A) provided with a slitted diaphragm and a small fluoroscopic screen (Patterson B); (3) electrical arrangement to transform the incoming commercial current into direct current of staggered voltages, and a device for rapid change of degree of amplification; (4) electric filter suppressing the flicker from the x-ray tube; (5) galvanometer transcribing the tracing to a moving film; and (6) microphone to be connected with a sound recorder (of the "stethocardiette" or a similar apparatus). (Fig. 1.)

Any upright fluoroscopic stand can be used for the seated patient; for very sick patients a horizontal fluoroscopic table is necessary. Any of the commercial tilt-tables can be used for both purposes. An x-ray machine with full-wave rectification is preferable because it is easier to suppress the 120-cycle ripple by filterage. Machines with half-wave rectification can also be used with a special filter for the 60-cycle ripple.

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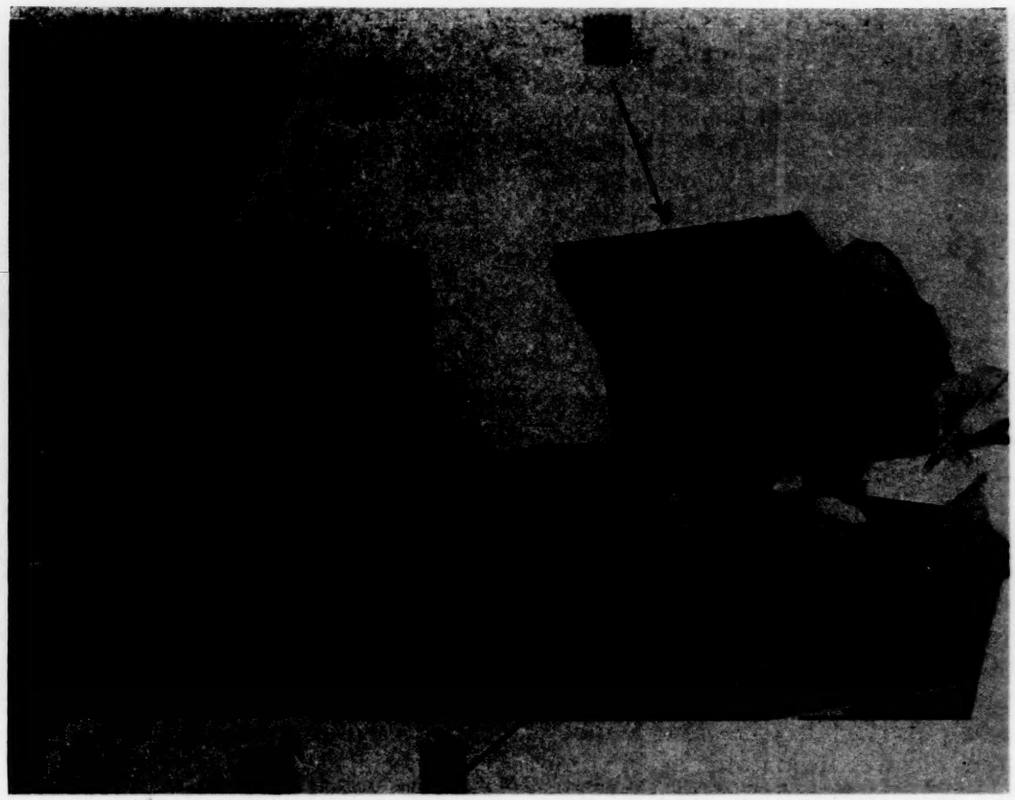


FIG. 1. Arrangement of the apparatus for fluorocardiography. (1) Pick-up unit behind the fluoroscopic screen; (2) box with regulating panel; (3) electrophonocardiograph. The patient is shown in the lateral position for recording the right ventricular tracing. (4) The microphone, placed on the precordial area, records the heart sounds.

The regulating devices described in (3) and (4) are built into a small portable box, 8 by 12 by 5½ inches. Any commercial electrocardiograph can be used. Since the authors apply the heart sounds as time reference, a "stethocardiette" (or similar apparatus) has been used as the recording machine. From the above description it is clear that most of the necessary equipment is already available in practically every hospital and in many private laboratories. The additional new equipment consists of the pick-up and regulating units, two small portable pieces of low cost.

While the classical roentgenkymograph registers the pulsating shadow directly on the film, in this new apparatus the pulsating changes of light energy, proportionate to the pulsating movements, are transformed into a pulsating electric current to be recorded by a standard electrocardiograph. This basic principle implies the possibility of using the same device for measurements of changes of density as a densograph; when the slit is placed over the center of an opaque object, the changes of opacity of the latter will be picked up and recorded.

The polarity of the apparatus is so arranged that an increase in light causes a downward movement of the tracing. Therefore, any drop of the curve indicates either an inward motion of the cardiac border (if the slit is across the border of the cardiac silhouette) or a decrease in the thickness of the structure (if the slit is over an homogeneous area, recording a densogram), both as a result of contraction. Any wave occurring before the first large vibration of the first sound is presystolic; any wave occurring after the last vibration of the second sound in diastolic; any wave taking place between the beginning of the first sound and the end of the second is systolic.

Fluorocardiography would appear to

have the following advantages over roentgenkymography: (1) The slit can be applied perpendicularly to the section of the contour to be studied and choice of place is possible under fluoroscopic control. This is extremely important in the oblique positions and has a special value in the postero-anterior position of the patient. (2) The speed of the fluorocardiographic film is much greater and this causes an apparent spreading of the different waves. Magnification of the height of the waves can be regulated at will. These two facts permit better individualization and study of the details. Furthermore, fluorocardiographic tracings record as many cycles as desired, another fact which facilitates study. (3) The timing of the waves is obtained in a simple and accurate way by comparing the tracing with a phonocardiogram simultaneously recorded.[32,33] (Chamberlain, Henny and Boone[23,24] time their tracings by simultaneous records of the carotid pulse, while Lian and Minot[20] prefer the electrocardiogram as a time reference.) (4) Fluorocardiography permits accurate study of the auricles, ventricles and large vessels in the oblique and lateral positions. (5) Fluorocardiography, through magnification, permits accurate study of changes in opacity of various organs (densograms) thereby permitting the study of "plethysmograms" of organs like the branches of the pulmonary arteries (hilar vessels), pulmonary veins and pulmonary parenchyma which could not be studied by roentgenkymography.

The procedure is performed by a two-man team, the fluoroscopist and the electrocardiologist. The "stethocardiette," electrical unit and pick-up device being assembled and the wire connection attached, the patient is seated on a rotating stool in front of the fluoroscope. An elastic strap is slung around his chest to hold the microphone which is placed over the center of the precordium in such a way as not to overlap the cardiac borders. Transmission of the heart sounds is checked with the audiophone. The patient is then instructed how to hold his breath in a medium position. The room is darkened as for any routine fluoroscopy, a screened pilot light illuminating the panel of the regulating unit and the electrocardiograph. With the patient in the postero-anterior position, the pick-up device is placed under fluoroscopic control in the region of the cardiac apex, the translucent slit being perpendicular to and crossing that part of the silhouette to be studied. With the slit in place and the fluoroscope in operation, the electrocardiologist regulates the amplitude of the deflections, then asks the patient to hold his breath and starts the electrocardiographic camera under constant observation and control of the light beam. After having obtained a good tracing of several heart cycles the operation is interrupted, the pick-up device moved to the next place desired and the same procedure repeated. Notes of the position of the patient, of that of the pick-up and of the degree of amplification used are made for every tracing.

A special electrical filter has been adopted for the simultaneous recording of electro- and phonocardiograms together with the fluorocardiogram in particular cases.

Several standard positions for the slit have been studied with the patient in both sitting and recumbent positions:[33,35] (1) *Patient in postero-anterior position* (Fig. 2): Apex, mid-left ventricle and high left ventricle; pulmonary knob; aortic knob; high and low right auricle; pulmonary veins (densogram); right and left hilar shadows (densograms); high, middle and low right and left lung fields (densograms). (2) *Patient in 10 degree left oblique:* Left auricular appendage; ascending aorta. (3) *Patient in 45 to 60 degree left obliques:* Left auricle; descending aorta (densogram); high, middle and low posterior ventricular border (left ventricle). (4) *Patient in 45 degree right oblique:* Left auricle; superior vena cava; inferior vena cava (in deep inspiration); upper border of diaphragm (liver tracing); high, middle and low anterior ventricular border (left ventricle). (5) *Lateral positions* (left lateral is preferred): Anterior ventricular border (right ventricle).

In most studies the fluorocardiograms were recorded during voluntary apnea in an intermediate phase because comparative observations had shown that the pulsations of the lung (and, to a lesser extent, those of the hilar shadows and the pulmonary

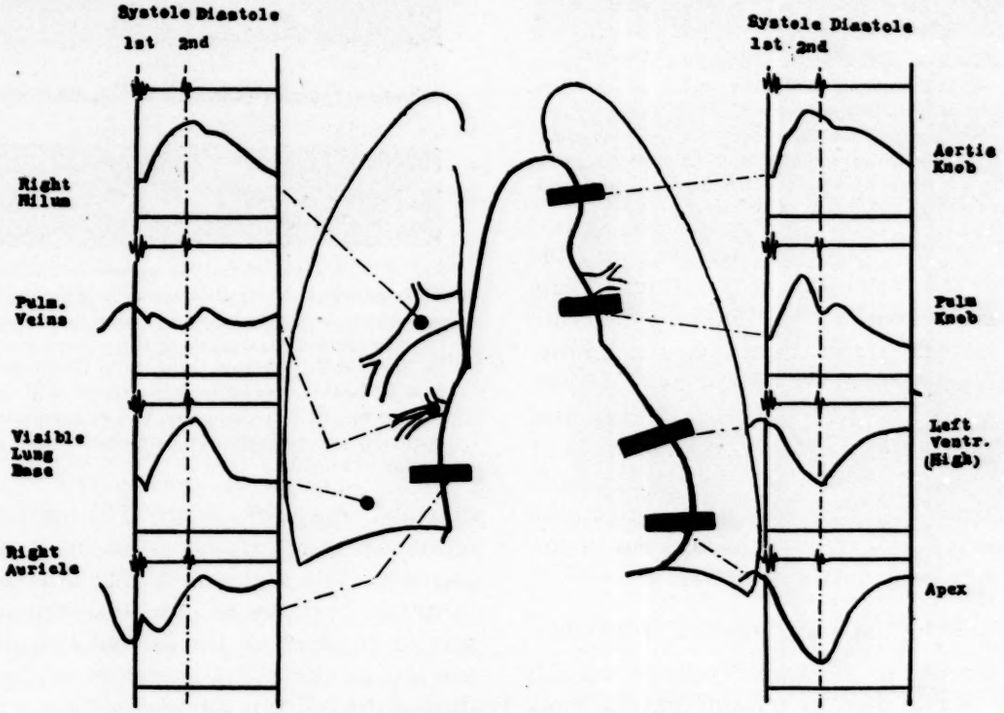


FIG. 2. Scheme of normal tracings recorded in the postero-anterior position.

artery) were greater in inspiration than in expiration. A few words of instruction usually suffice in teaching the patients to hold their breath without excessively inflating or deflating their lungs. By using this procedure, however, it was difficult to obtain reliable tracings in children and in patients with chronic diseases of the lungs, who were unable to control their respiration because of either age or dyspnea. This difficulty was overcome by the following technical means.[42] Wandering of the base line caused by respiration may be considerably reduced by altering the electrical time constant of the apparatus. When this constant is shortened, there is a proportionally greater attenuation of the coarse waves as compared to the more rapid. Respiration is represented in the fluorocardiogram by extremely slow waves, far coarser than any of the waves due to cardiac action. A suitable condenser introduced between the fluorocardiograph and the recording galvanometer is sufficient to modify the time constant of the apparatus. The smaller the condenser the lesser is the electrical constant. Various size condensers, which may be selected by means of a switch, permit the operator to obtain the optimum time constant, namely, a value which produces a fluorocardiogram that does not wander off the paper.

The reduction of the electrical time constant of the apparatus does introduce a certain degree of error in the fluorocardiogram which is dependent upon the amount of reduction. The error presents itself in two forms: one is a slight error in the phase (or actual time) of registration of the component waves; the other is a slight change in the configuration. However, no elimination of the component waves which would be present under normal operating conditions was observed.

Using the above described filter comparative studies in normal subjects were

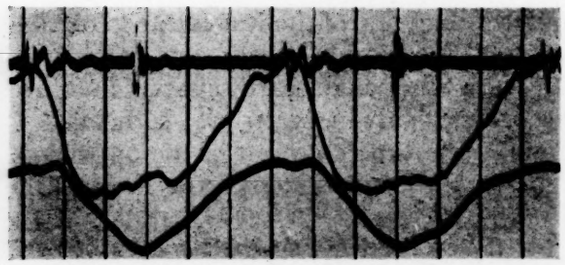


FIG. 3. Simultaneous fluorocardiograms of the apex (middle curve) and of a higher point of the left ventricular profile (lower curve). Phonocardiogram: The apical tracing initiates its drop at the beginning of the tension period while the higher ventricular tracing (lower curve) shows a notch in that phase and drops only at the beginning of the ejection period.

made.[42] It was proven that it is possible to record the pulsations of the lungs or any other cardiovascular or pulmonary structure during normal respiration with the following precautions: (1) Whenever possible, the subject is instructed to breathe evenly and slowly, without sudden gasps. (2) The roentgenologist should observe the visible structure which is being studied and make sure that it is not moving in and out of the slit because of respiratory dynamics.

TYPICAL TRACINGS IN NORMAL SUBJECTS

The tracing of the apex[33] reveals a small positive wave due to completion of ventricular filling by the auricular contraction; a small negative wave caused by torsion of the heart during the tension period; a deep negative wave during the ejection period of systole; a rapid rise in early diastole; a slow rise during middle and late diastole. (Fig. 2.) Tracings recorded over any point outside the apex usually present somewhat smaller waves and seem to start later than the apical tracing. The last fact is due to less marked interference of motion phenomena and gives the impression that the contraction starts at the apex and spreads toward the base. (Fig. 3.) Return of the ventricular mass to its position in diastole may cause non-coincidence of the deepest point with the second sound. This phenomenon, however, is more marked at the apex and may be entirely absent. Occasionally a slow rise or a slower course, even simulating a small drop in early

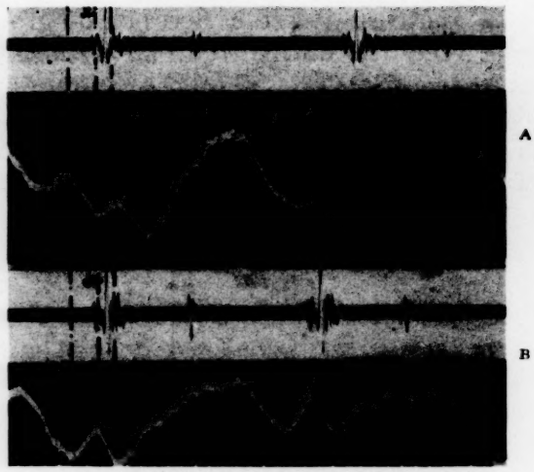


FIG. 4. A, tracing of the left auricle in the left oblique position. A negative wave is present in presystole in a normal subject because of auricular contraction. B, tracing of the pulmonary veins in the postero-anterior position in the same subject. A positive wave (*a* wave) is present during presystole. Line x indicates the initiation of the auricular waves (negative presystolic wave in the venous tracing).

diastole, may be seen. The latter phenomenon is probably due to positional changes. The tracings of the anterior and posterior surfaces of the left ventricle are similar to those of the lateral margin. The tracing of the right ventricle is similar to that of the left but the waves have a smaller amplitude.

Both left and right auricular tracings reveal first a deep negative wave resulting from the auricular contraction (Fig. 4A), then a second decrease of auricular volume due to ventricular traction over the A-V septum and later an early diastolic drop. If the subject is in the recumbent position, a gradual rise in the tracing of the right auricle may be seen during systole on account of the greater venous return from the inferior cava.

The tracing of the ascending aorta[35] reveals first a small negative wave due to traction of the left ventricle over the root of the vessel, then a rapid rise and a sustained plateau similar to a tracing of intraventricular pressure, later a high wave in diastole due to summation of the dicrotic wave with a movement of return of the vessel to its prior position. A small positive

wave may be seen occasionally in presystole due to motion of the heart at the time of auricular contraction.

The tracing of the aortic knob[33] has all the characteristics of a "central" pulse. That of the pulmonary knob presents a smaller anacrotic depression and a higher dicrotic wave, often resembling the tracing of a peripheral pulse. (Fig. 5A.)

The tracing of the descending aorta[33] usually presents a rounded profile and no trace of the dicrotic wave; the fact that the tracing is a densogram may explain the lack of details.

The tracing of either hilar shadows[33,35] reveals an arterial wave which starts with a definite delay over that of the pulmonary knob; it has a rounded profile, a peak which is near the second sound and may or may not present a dicrotic wave. (Figs. 2 and 5B.)

The tracing of the pulmonary parenchyma[33,35] (Fig. 5C) is equivalent to a plethysmogram. The ascending branch of the wave is purely arterial; the rise of the wave occurs with a certain delay over that of the respective hilar vessels. On the other hand, the peak and the descending branch of the wave are deeply affected by variations in the venous filling of the lung. Actually the peak occurs soon after that vibration of the phonocardiogram which records the opening of the mitral valve. The descent of the tracing is rapid on account of the forward motion of the pulmonary venous blood toward the heart in early diastole which causes depletion of the venous network.

The pulmonary veins can be studied by applying the slit transversely over an area which is about 2 cm. outward from the convexity of the right auricle in the postero-anterior positions.[35] This point was indicated by Marchal[21] as corresponding to a bundle of pulmonary veins and this was confirmed by timing the arrival of diodrast on a fluorocardiogram. A thick vascular shadow is visible at times in that area.

The arrangement of the larger vessels of the hilar region is different for the arteries and the veins. It has been known that

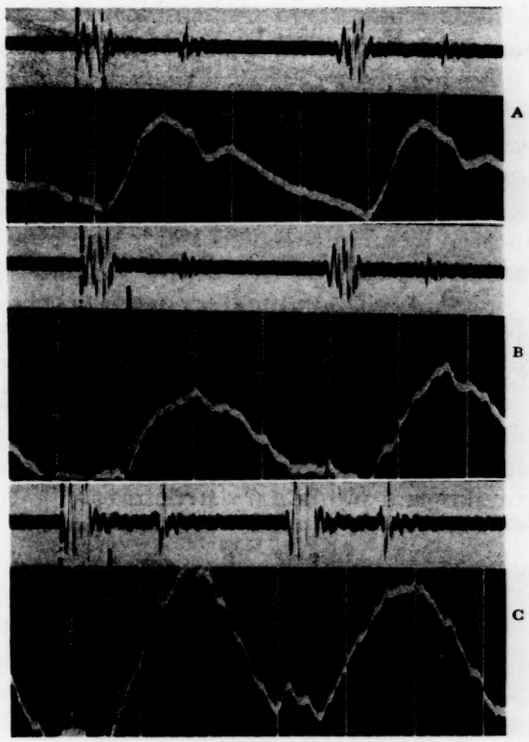


FIG. 5. The arterial wave in the pulmonary circulation in a normal subject. A, pulmonary knob; B, right hilum; C, visible base of the right lung. These tracings have been taken with different degrees of amplification, minimal amplification being used for the pulmonary knob (A) and maximal amplification for the peripheral lung field (C).

veins coming from the middle and lower lobes on the right, in their almost horizontal course, occupy the space between the right heart border and the lower portion of the right hilar shadow thus providing an area mainly occupied by veins. Tracings recorded over this "venous field" present a typical "venous" pattern.[35] They show a positive presystolic wave ("a" wave), an early systolic collapse and a gradual rise which culminates at the time of mitral valve opening ("v" wave). (Fig. 4B.)

A satisfactory tracing of the superior vena cava[33] is seldom recorded in normal subjects, young or old. It is more commonly recorded if there is venous engorgement. On the other hand, the tracing of the inferior cava[33] is obtained frequently in deep respiration. It shows a positive wave in presystole, a deep systolic collapse and a

diastolic collapse. It resembles the mechanical tracing of the liver.

Fluorocardiogram of the Child. The infantile fluorocardiogram can be obtained by using the aforementioned filter.[42] It still presents occasional irregularity or wandering of the base line due to the fact that children frequently have a sudden onset and end of inspiration with an abrupt change in phase. As a result the filter cannot prevent entirely a slight wandering of the base line because the speed of the respiratory wave is similar to that of the cardiac waves. In spite of this, perfectly visible cardiac waves can be obtained over all those cardiovascular and pulmonary structures.

SPECIAL STUDIES OF NORMAL PHYSIOLOGY

Velocity of the Arterial Waves in the Pulmonary Circulation. The velocity of the pulse waves in the lesser circulation has been studied in ten subjects by comparing the tracings obtained by placing the slit first over the pulmonary knob, then over the right hilar shadow and later at the visible base of the right lung.[35] (Fig. 5.)

The average times of arrival of the pulse waves are 0.08 second for the pulmonary knob, 0.12 second for the right hilum and 0.16 second for the visible base of the right lung. These data were obtained by measuring the distance on the tracing from the beginning of the first sound to the foot of the wave. Correct figures are about 0.06 second lower because the opening of the pulmonic valves takes place later than the beginning of the sound.

Considering the distances travelled by the pulse wave, the authors calculate a velocity of the pulse waves of 2 M. per second between pulmonary knob and right hilus, and 2.75 M. per second between right hilus and visible base of right lung. While the speed of the pulse in the lesser circulation is less than in the greater, being roughly one-third of the latter, the pulse increases its speed in the small, less extensible arterioles both in the lesser and in the greater circulation.

Temporal Relationship between the Contractions of the Right and Left Heart. Knowledge of the normal temporal relationship of contraction of the two auricles and ventricles is important in various clinical conditions, like bundle branch block, Wolff-Parkinson-White syndrome and interauricular disturbances. Ellinger, Gillick, Boone and Chamberlain[25,29] found no constant time relationship between the action of the right and left heart in healthy individuals indicating that the right heart may precede the left heart by up to 0.03 second or lag behind 0.01 second.

In order to obtain a double simultaneous tracing two apparatus for fluorocardiography and a "Tri-Beam Stethocardiette" were used. Observations were made on eight normal subjects between the ages of fourteen and forty-six.[34] The two ventricles were studied in the left lateral position applying one slit as low as possible across the anterior border of the cardiac shadow (right ventricle) and the other across the lower posterior border (left ventricle). The two auricles were studied with the subject in the right oblique position by applying the slits, one below the right bronchus (left auricle) and the other much lower (right auricle). The pulsations of the pulmonary arch and of the aortic arch were studied with the subjects in the postero-anterior position by applying the slits of the two pick-up units across the borders of the curves corresponding to the two large vessels.

The various observations concerning the temporal relations in cardiac action confirm each other. The final conclusions concerning the time relationship of the ventricular pulsations are based on the correlation of tracings obtained from the auricles (indicating the opening of the A-V valves), from the ventricles (showing the beginning of ejection from both ventricles) and from the large vessels (revealing the initial rise of the aortic and pulmonic pulses). The evidence indicates that the right ventricle contracts first and the interval between the contractions of the two ventricles is between

0.025 and 0.030 second. (Fig. 6). The same interval exists between the pulmonic and aortic pulses. These results indicate an interval which is larger than that found by experimentation on animals. This is partly due to the fact that we measure the intervals between the beginning of ejection of the two ventricles and not between the actual initiation of two systoles.

Observations on the pulsations of the auricles indicate that here, too, there is a brief interval, the right auricle contracting before the left. Our observations, therefore, are consistent with known physiologic facts.

Isometric Relaxation Period of the Left Ventricle. The study of this period is important for both physiologic and clinical studies as it represents the interval between the closure of the aortic valve and the opening of the mitral valve. Several attempts have been made to measure this period in normal subjects by means of arterial and venous tracings or by observation of electrokymograms.[28] A phonocardiographic study with simultaneous recording of phonocardiograms and fluorocardiograms led Luisada, Romano and Torre[38] to the conclusion that previous figures were too high. Their findings varied between 0.04 and 0.07 second in normal subjects and between 0.07 and 0.11 second in patients with mitral stenosis. They also were able to demonstrate that the small rebound which may be observed occasionally in the tracing of the left ventricle is entirely in the early diastolic phase and starts *after* the opening of the mitral valve.

Attempts at Measurement of Blood Pressure in the Lesser Circulation. In a brief note[22] Marchal suggested the use of the fluorocardiogram of the lung (called by him "kinedensigram") for the measurement of blood pressure in the lesser circulation. He tried to reduce the pulsations of the lung by means of an elevation of the intrapulmonary pressure. To this end, he had the patient expire forcibly into a manometer and the complete extinction of the pulmonary pulsation was taken as an indication that the systolic pressure of the pulmonary

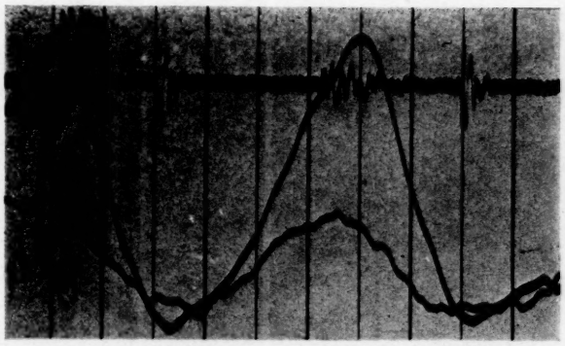
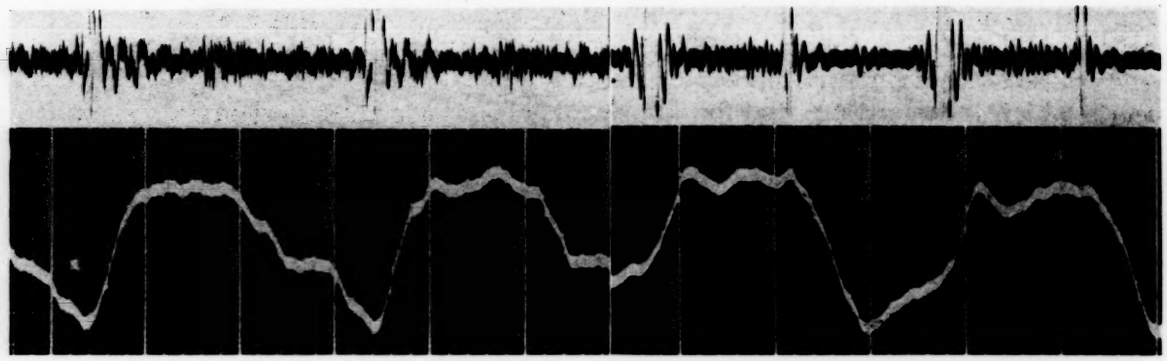


FIG. 6. Simultaneous tracings of the right and left ventricles in the left lateral position. The right ventricle contracts before the left. The upper tracing is a phonocardiogram.

arterioles had been reached by the air of the alveolar cavities. The method, if successful and accurate, would permit the measurement of pressure in the lesser circulation without danger to the patient. Therefore it deserved control. Several series of experiments were performed.

Using a valve which permitted controlled alteration of the positive pressure against which the subject was exhaling, several experiments were performed. High expiratory pressures were followed first by a decrease of the positive pulmonary pulsations, then by their transformation into negative waves.[42]

The transformation of the tracing, which was followed in some cases by complete disappearance of any pulmonary pulsation, occurred only for pressures of 35 to 50 mm. Hg. As the latter are definitely too high for pulmonary arterial pressures, two possibilities were considered: (1) That the subject may not expire when the pressure of the bottle is higher than that which he can reach. Marchal admitted this possibility. Then the pressure of the manometer does not correspond to that of the respiratory passages. (2) That the pressure of the pulmonary artery is raised temporarily by the increase of the intra-alveolar pressure. In order to check this tests were made on experimental animals.[41] The trachea of an anesthetized dog was connected with the bottle by the valve device already tested in man; the pressure of the right ventricle was



7A 7B

FIG. 7. Tracings of patients with mitral stenosis and insufficiency. A, a patient with sinus rhythm. The negative wave is in presystole (x); the positive plateau is in systole. B, a patient with auricular fibrillation. There is an absent presystolic wave and a positive systolic plateau.

recorded by means of a venous catheter and a Sanborn electromanometer. The ventricular tracing indicates that when the animal expires against pressure, the diastolic pressure of the right ventricle rises becoming positive (increase of residual blood?) and that the systolic pressure rises even further, reaching a level which is over 40 per cent higher than the normal level. This result, in our opinion, invalidates the accuracy of the method for clinical purposes.

OBSERVATIONS IN CLINICAL CONDITIONS

Dynamics of the Left Auricle and Pulmonary Veins in Mitral Valve Lesions. The effects of mitral valve lesions on the left auricle have been studied by numerous authors using different methods (auscultation, inspection and palpation, esophagocardiography). Fairly accurate observations of motion changes of the left auricle have been made in the past by fluoroscopy and roentgenkymography.[17] Fluorocardiographic studies have confirmed and amplified those observations.[36] The authors studied twenty-three patients with lesions of the mitral valve. Correlation of the clinical diagnoses, the phonocardiographic findings and the fluorocardiographic tracings led to the following conclusions: (1) In patients with mitral regurgitation or double mitral lesion there is always a positive systolic plateau. (2) In patients with mitral stenosis and no clinical evidence of insufficiency (no systolic murmur) a typical systolic plateau is also present. (3) The plateau is typical both in cases with sinus rhythm and in those with auricular fibrillation. (Fig. 7.)

The typical pattern in the fluorocardiographic tracing of the left auricle in patients with mitral valvular disease is due to the regurgitation of blood from the left ventricle into the left auricle during ventricular systole. It consists of a rectangular positive "plateau" and resembles both the tracing of intraventricular pressure and that of the left auricle in animals with experimental lesions of the mitral valve.

Another abnormal feature was found in tracings from patients with mitral stenosis and sinus rhythm; this consists of an abnormal form and depth of the auricular wave which was small, irregular and often difficult to visualize. This abnormality may be attributed either to slow emptying of the left auricle because of marked mitral narrowing or to weak left auricular contraction caused by muscle damage in the left auricle.

In conclusion, the fluorocardiogram of the left auricle in mitral valvular disease typically demonstrates a positive plateau (regurgitation during ventricular systole). This is even more pronounced in instances of auricular fibrillation and thus may be of diagnostic value even in the absence of any apical murmur.

In addition, the tracing of the pulmonary veins presents an abnormal and typical pattern in those instances in which the left

auricular tracing shows a plateau. This pattern consists of; (1) high positive auricular wave in presystole if there is sinus rhythm; no auricular wave if there is auricular fibrillation; (2) typical positive plateau in systole similar to that of the left auricle. This proves that the regurgitation of blood from the left ventricle into the left auricle either continues back into the pulmonary veins or causes an increase of pressure and volume in the latter which faithfully reproduces the curve of pressure (and volume) of the left auricle, as was expected theoretically.

Tracings of the Left Ventricle in Myocardial Infarction. The abnormal movements of the left ventricular wall following myocardial infarction have been repeatedly investigated by means of roentgenkymography.[7,11–17] The most common abnormalities described were diminution or absence of pulsation in a segment of the left ventricular contour, systolic expansion over the lower left contour and diastolic splintering. While most observations were made with the patient in the postero-anterior position, some were made also in the oblique positions.[12]

Luisada and Fleischner[37] have studied twenty cases of myocardial infarction. The patients were studied in the sitting position if the lesion was old and in the recumbent position if the lesion was recent. The left ventricle was studied first in the postero-anterior position, then in both obliques (a 40 degree right oblique permits observation of the anterior wall; a 60 degree left oblique, of the posterior wall of the left ventricle). In each of these three positions the study started by applying the slit over the lowest point above the diaphragm or, if the lower profile of the heart was visible through the gastric fundus, over the most medial point of this. Then several different points were studied along the contour of the left ventricle from its lowest to its highest part. The same procedure was repeated in the oblique positions.

Various abnormalities have been observed. Some of them have been found typical of circumscribed damage to the ventricular wall; others are not specific and may be observed also in cases of diffuse myocardial damage.

Various abnormal patterns were observed during systole. Four of these can be grouped together, being an expression of various

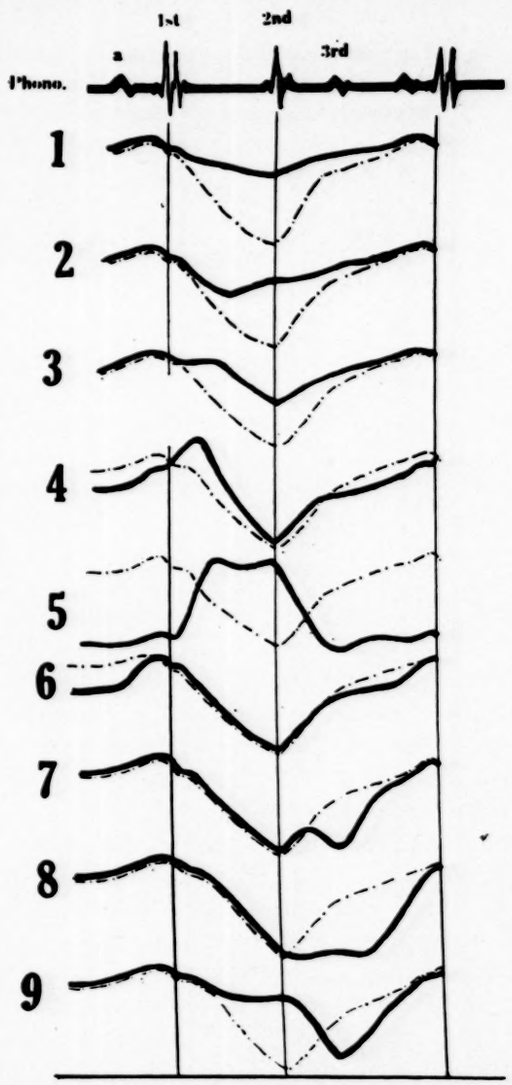
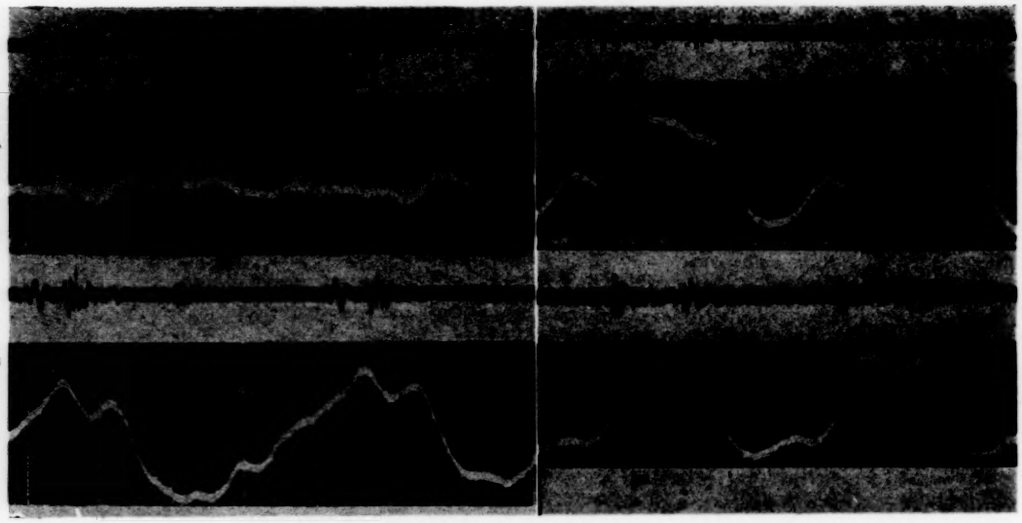


FIG. 8. Scheme of the major abnormalities of the ventricular tracing (continuous line) compared with the normal tracing (dotted line) in myocardial infarction. (1) Decreased amplitude of the ventricular wave; (2) early end of the ventricular wave; (3) late onset of the ventricular wave; (4) early systolic distention followed by normal contraction; (5) systolic distention (dynamic aneurysm); (6) marked presystolic distention; (7) early diastolic rebound; (8) late distention in diastole; (9) decreased amplitude of the systolic wave followed by early diastolic drop.



9. 10.

FIG. 9. Tracings of the anterior left ventricular wall in the left oblique position. Old anterior myocardial infarction present. Local paralysis (A) compared with a tracing recorded one step lower (B) which indicates a strong contraction.
FIG. 10. Dynamic aneurysm; inverted or "paradoxical" pulsation with formation of a positive plateau in two cases (A and B) of old myocardial infarction.

degree of the same phenomenon, namely, reduced amplitude, early end or late onset or absence of the ventricular wave. (Figs. 8 and 9.) Two other systolic patterns express a greater or lesser tendency toward distention, namely, early distention followed by normal ventricular wave or inverted pulsation (so-called paradoxical pulsation). (Figs. 8 and 10.) Various abnormal patterns were also observed during diastole, such as a marked rebound, absence of rapid rise or drop of the tracing in early diastole. (Fig. 8.)

In four of the authors' cases the electrocardiogram indicated posterior myocardial infarction; in all of these the abnormality of contraction demonstrated by fluorocardiography was located in the posterior wall and extended to the lateral wall. In eight cases the electrocardiogram indicated anterior or anterolateral myocardial infarction. In six of these the abnormality of contraction was located in the anterior wall and extended to either the apex or the lateral wall; in one case (incompletely studied) a posterolateral abnormality was found; in one no abnormality was observed. In seven cases there was a history of repeated attacks of myocardial infarction or of attacks of severe, prolonged, precordial pain; in all of them marked abnormalities of contraction were found in the anterior, posterior and lateral wall. There is thus almost 90 per cent agreement between electrocardiogram and fluorocardiogram as to location of myocardial infarctions. (Fig. 11.)

Two abnormalities of the systolic wave have been considered diagnostic of localized myocardial damage, in the majority of instances this being identical with myocardial infarct: (1) Reduced amplitude of the ventricular wave or disappearance of this wave in a circumscribed region of the left ventricle. Whenever the surrounding areas present large waves, this sign is definitely related to infarction. As that area is functionally (and usually also anatomically) excluded from participating in active contraction, the authors suggest the name of local paralysis for the phenomenon thus revealed by fluorocardiography. (2) Inverted pulsation (paradoxical pulsation) of a circumscribed area of the ventricular myocardium. In typical cases this inverted pulsation assumes the aspect of a plateau,

indicating that the inert wall is passively distended by intraventricular pressure. This type of pulsation may be associated with the existence of a well defined bulge of the ventricular silhouette on chest films. In such cases the term ventricular aneurysm is commonly used. In other cases the bulging occurs only in systole while no bulge is present in diastole. This phenomenon, occasionally observed on fluoroscopy, is hardly noticeable on roentgenograms; these, even if taken at the maximum of systole, would show but a minute projection hardly detectable without simultaneous observation of the two opposite motions. The dynamic significance of such an inverted pulsation is similar to that of an aneurysm. The wall distends in systole absorbing part of the dynamic effort of the normal myocardium; it collapses in diastole, disturbing the normal filling and spilling its retained blood into the rest of the ventricular

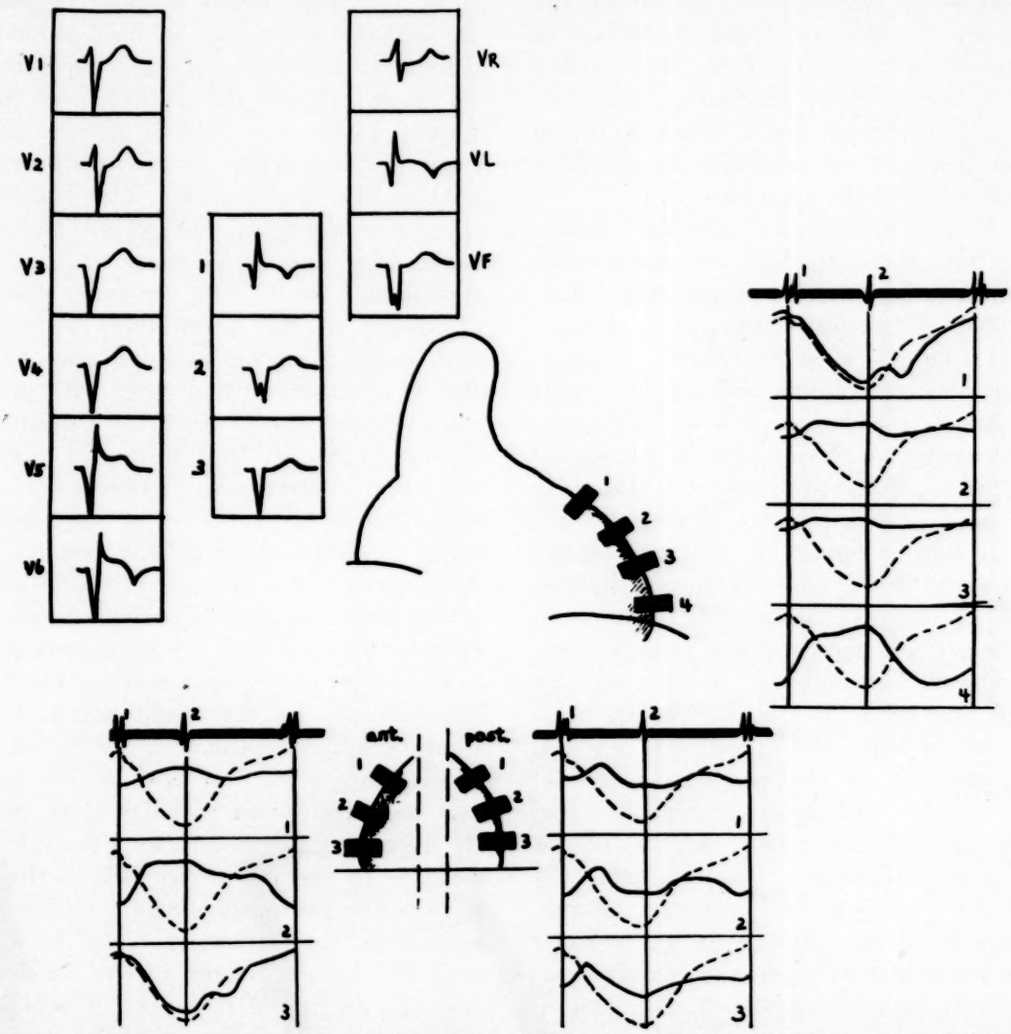


FIG. 11. Diagrammatic locations of the positions of the slit and topographic reconstruction of the morphologic changes in a patient with multiple myocardial infarctions. Dynamic aneurysm extends from the apex to the anterior wall. There is local paralysis above the apex as well as multiple abnormalities of contraction in the posterior wall. There were two older and one recent attack of anterior infarction. Electrocardiograms taken of the limb leads, unipolar chest leads and unipolar limb leads. The schematic tracings on the right side of the figure refer to the fluorocardiograms recorded over the left ventricle in the postero-anterior view (central sketch); those at the bottom refer to tracings recorded over the anterior and posterior wall, respectively, in the oblique positions.

cavity. This similarity may justify a new term, dynamic aneurysm, for instances in which a typically inverted pulsation is found without any persisting bulge in the profile of the left ventricle.

Both lack of pulsation and inverted pulsation were encountered on either the anterior or the posterior wall, or in one of these locations extending to the lateral wall or in a larger area including anterior, lateral and posterior walls. Most common is either anterior or posterior localization with extension to the lateral wall.

Studies in Uncomplicated Cardiac Shunts. The authors have studied ten such cases between the ages of thirteen and thirty-five. These were all patients presenting characteristic clinical, roentgenologic, electrocardiographic and phonocardiographic findings. Five had a patent ductus arteriosus while the other five had a ventricular septal defect. Speed, shape and height of the pulse waves were studied.[42] (1) The study revealed a higher speed of the pulmonary arterial wave in the cases of patent ductus; normal or slightly abnormal figures in septal defect. (2) Shape of the pulse waves: This can be studied by measuring the distance foot-peak in the waves. In both groups of patients the pulse was normal (patent ductus) or slightly tardus (septal defect) in the pulmonary knob; it was celer (more so in the patent ductus) in the hilum and pulmonary parenchyma. (3) Height of the pulse waves: In patent ductus arteriosus the pulse wave in the pulmonary knob is frequently as high as or higher than the pulse in the aortic knob. In ventricular septal defect the pulmonic pulsations are higher than the normal but smaller than those of the aorta. The peripheral pulmonic pulses (hilar and parenchymal) are increased in height in both defects but less so in ventricular septal defect.

Even if no typical abnormality was revealed by this study, the diagnosis of the two types of shunts (patent ductus and ventricular septal defect) and the differential diagnosis between them may be made easier by fluorocardiography. Moreover, the finding of a normal left auricular tracing in a patient with a loud systolic murmur is an indirect indication of a septal defect.[36]

Studies in Chronic Cor Pulmonale. The authors first studied six patients with only mild dyspnea who, despite chronic cor pulmonale, were able to hold their breath during the recording of fluorocardiograms.[42] In these subjects the pulsation of the pulmonic knob was found greater than in normal subjects and sometimes larger than that of the aortic knob. The pulsation of the hilar shadows was found abnormally high, occasionally as great as that of the pulmonary knob. On the other hand, the pulsation of the pulmonary parenchyma was found abnormally small and, at times, not recordable. In two cases with predominant lesions of one lung the pulsation was imperceptible in that lung but normal in the other. Differences between the various lobes have been observed in cases with lobar predominance of the lesions. These findings reveal a decreased vascularization of the lungs (or part of them) caused by the chronic process and an increased pressure in the larger vessels as a result of the reactive hypertrophy of the right ventricle (pulmonary hypertension and cor pulmonale).

In another patient with severe dyspnea due to emphysema tracings were recorded by using the aforementioned filter.[42] It was possible to observe the details of the pulsations of the pulmonary artery which had an extremely high dicrotic wave in contrast with the simple profile of the aortic pulse. Also, by means of the filter, it was possible to record a fair pulsation at the base of one lung, no pulsation at that of the other. This coincided with the physical and roentgenologic findings of emphysema which was predominant on one side.

Aortic Aneurysms and Mediastinal Tumors. Differential diagnosis between these two conditions is a problem which frequently confronts the roentgenologist. Both in the case of a mediastinal tumor and in that of an aortic aneurysm the shadow of the mass may pulsate. In the first instance the

pulsation is transmitted; in the second it is due to the expansion of the pouch. While a border fluorocardiogram may not be able to differentiate between the two lesions because in both cases the border will move with a pulsation of arterial type, theoretically a densogram of the shadow would permit easy differentiation. In the case of a tumor the mass is solid and poorly provided with vessels while in the case of an aneurysm the whole mass is full of blood and expands in systole, increasing its thickness.

A study was made in two cases of mediastinal tumors, in two cases of diffuse dilatation of the aorta and in one case of aneurysm of the junction between aortic arch and descending aorta. The tumors gave densograms which revealed only minute, irregular pulsations. The cases with diffuse dilatation and that with the aneurysm gave densograms which are absolutely identical in shape with the border tracings in the same cases and nearly as high. This demonstrates that fluorocardiography may be used for the differential diagnosis between the two conditions. Even in the case of an aneurysm full of clots it is likely that some part of the pouch still communicates with the lumen of the aorta; this should be sufficient to cause an expansive pulsation of the pouch and to give a densogram of arterial type.

Contractions of the Right and Left Auricles in A-V Block. Study of auricular contractions in these conditions requires simultaneous recording of three tracings, the fluorocardiogram, the phonocardiogram and the electrocardiogram. Recording the electrocardiogram while the patient is examined by x-ray requires a special attenuator (or filter) to prevent flickering of the base line. This was previously described by us[31] and was employed for this particular study. Electrocardiograms also have been taken by others[20,30] using different technical devices.

The profile of the isolated auricular wave is similar in both the right and the left auricles.[42] It is much simpler than when the auricular is followed by a ventricular contraction, on account of the interference of the latter with the auricular volume. The auricular wave consists of a rapid drop followed by a slower rise and closely resembles the profile of a ventricular wave recorded over the border of the left ventricle. This observation is not in full agreement with those of others[30] who called a "pure" auricular curve that actually showing very little result of the auricular contraction.

The actual degree of emptying of the auricular chambers can be observed and it is possible to see the influence of ventricular contraction on the subsequent auricular tracings.

MISCELLANEOUS OBSERVATIONS

Arteriovenous Fistula. One such case was studied by recording the tracings of the left ventricular margin. Manual occlusion of the femoral fistula led instantaneously to bradycardia and to a remarkable increase in the amplitude of the ventricular wave; the latter fact was not revealed by either fluoroscopy or serial chest films.

Pericarditis with Effusion. One case was repeatedly studied. During the stage of effusion no visible wave was recorded on any point of the pericardial contour. After paracentesis and introduction of air typical but somewhat small waves were recorded over the left ventricular and right auricular borders above the fluid level. The fluid level itself pulsated and presented a typical ventricular pattern on the left and an auricular pattern on the right. After complete recovery normal tracings were recorded.

Bundle Branch Block. Observations in this field have been made by Ellinger and his co-workers.[29]

OTHER POSSIBLE APPLICATIONS

This review has been based predominantly on the observations made by one group[31–42] since the beginning of their studies about three years ago, although it also covers all other available reports. These early results in the field of physiology and practical clinical application are encouraging. More

is to be expected from continued work and the activity of other groups with this and related methods.

It would seem that the method of fluorocardiography, which is flexible, easy of performance and requires but a small investment in apparatus, deserves wider exploration for its value in pathophysiologic studies and for its clinical usefulness.

SUMMARY

Studies of technic, observations on normal subjects and first clinical applications of a new method are reported. The method permits inscription on a continuous film of either the motions of the border of the cardiovascular silhouette, as observed on the fluoroscopic screen, or the changes in density of the cardiovascular shadows. The method in general is called fluorocardiography; the two types of tracings are termed border tracings and densograms, respectively.

Various tracings and their physiologic interpretations are given in detail.

Studies of cardiovascular physiology are reported; among these are one on the temporal relationship between the contractions of the right and left heart; one on the velocity of the arterial pulse wave in the pulmonary circulation; one on the isometric relaxation period of the left ventricle; and one on pressure recording in the pulmonary artery.

The results of two systematic clinical studies are reported, one in mitral valve lesions, the other in myocardial infarction. In addition, various clinical observations are reported including cases of uncomplicated shunts, cor pulmonale, pericarditis, heart block, aortic aneurysms and others.

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Seminars on Congestive Failure

Dynamics of Congestive Heart Failure*

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CONGESTIVE heart failure involves all parts of the heart and circulation. In an analysis of this condition it may be useful to enumerate the main physiologic components of this complex apparatus:

1. Intrathoracic and intra-abdominal great veins and right auricle: the systemic venous reservoir. This contains, in normal conditions, a generous volume of blood under low tension, such that normal stroke volumes of 70 cc. or 80 cc. are removed at each heart cycle, under resting conditions, with only a 3 mm. to 5 mm. change in the right auricular pressure.[1]

2. Right ventricle: The volume of blood in the normal right ventricle is not accurately known; it is probably somewhere in the neighborhood of 50 cc. at the end of systole and thus about 130 cc. at the end of diastole.[2] Systolic right ventricular pressure averages 25 mm. Hg, the end diastolic (filling pressure) 1 to 3 mm. Hg.[1]

3. Pulmonary artery: Systolic pressure averages 25 mm. Hg, with a normal range of 18 to 30 mm. Hg, the diastolic pressure is about 8 mm. Hg.

4. Pulmonary capillaries: Pressure in these vessels has been recorded from 7 to 15 mm. Hg.[3]

5. Pulmonary veins and left auricle: the pulmonary venous reservoir. This is apparently a less voluminous and less distensible blood reservoir than that on the right side as the pressure changes during the cardiac cycle are much wider.[4] Normally the pulmonary vascular system is thought to contain some 300 to 500 cc. of blood. The mean left auricular pressure is about 4 mm. Hg higher than that of the right auricle.[4]

6. Left ventricle: There apparently is residual blood in the normal left ventricle at the end of systole,[5] and the volumes may be presumed to be similar to those in the right ventricle; systolic pressure 120 ± 20 mm. Hg; the end diastolic pressure is probably a few mm. Hg higher than that in the right ventricle.[4]

7. Coronary circulation: There is very little factual information about coronary blood flow in human beings although such studies are now in progress.

8. Systemic aorta, arteries and arterioles: This elastic system, with its systolic pressure of 120 ± 20 mm. Hg and diastolic (in the brachial arteries) around 75 mm. Hg, maintains a flow of blood to tissues throughout the cardiac cycle. There is an extraordinarily effective and sensitive reflex mechanism regulating over-all arteriolar tone, or "peripheral resistance," tending in general to maintain an approximately constant blood pressure in spite of wide changes in cardiac output and in regional blood flows.

9. Systemic capillaries, systemic veins: Here also there are constantly active vasomotor adjustments, both local and regional, in accordance with tissue needs. McMichael,[2] in his paper in the present series, stated admirably the case for both the existence and the importance of venomotor tone as a factor in cardiocirculatory dynamics.

10. Blood depots, shunts: It is important to realize that there are in the systemic circulation large regional volumes of blood that can be shifted, at need, into the central

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(intrathoracic) venous reservoir and can be maintained there and then shifted away again. The Valsalva experiment results in a large overdistention of all great veins with blood whether or not the arterial blood pressure falls.[6] Pericardial tamponade and other central venous obstructions do the same thing, such distention being also sustained. In muscular exercise all visible veins are full of blood while at the same time arteries and arterioles are also dilated. Just where in the periphery this distending blood volume comes from is not clearly known. Krogh's idea[7] that the splenic-portal-hepatic system is the chief mechanism which shunts blood into the general circulation apparently is true for the dog,[8] but there is no good evidence that this mechanism operates in man.

The aforementioned is in a sense only an extension of the general notion of vasomotor tone, but it is a special aspect of this function and deserves emphasis. Certainly nothing is further from the truth than the oversimplified concept that the circulation consists of an arterial tube and a venous tube, with a resistance between and a pump, the heart, driving fluid around the circuit and that blood volume shifts can only be from arterial tube to venous tube, or *vice versa*.

11. Renal circulation: This controls salt and water balance and thus ultimately tissue and blood volumes. The significance of this function in congestive heart failure has been extensively covered in other papers of this series.[9,10,30]

Performance of Normal Circulation in Exercise. A knowledge of the action of the normal heart and circulation, especially under conditions of stress, is essential to an understanding of the physiology of congestive heart failure.

In physical exertion of moderate degree, oxygen consumption will be increased from 300 cc. per minute to 1,800 cc. per minute. To provide the tissues with oxygen there will be something like a two-fold increase in arteriovenous oxygen difference and a three-fold increase in cardiac output. The latter is usually accomplished in part by increase in heart rate and in part by increase in stroke volume.

At this increased level of blood flow, systemic arterial blood pressure normally increases but not greatly; pulmonary arterial pressure is not increased at all;[11] indicating in both pulmonary and systemic circuits a marked "compensatory" arteriolar dilatation and decrease in peripheral resistance.

Venous pressures during exercise, or more exactly the effective or "net" filling pressures at the end of diastole in the right and left ventricles, are difficult to ascertain. Earlier studies described increase in peripheral venous pressure, up to about 130 mm. saline, during exercise; more recent work suggests that there may be little rise or even a fall.[2] The actual "net filling pressure" in the right ventricle, that is, the effective pressure within the thorax, can only be determined by simultaneous measurements of intraventricular and intrathoracic pressures, and this has not been done in exercise in human subjects. Such measurements have been made in a few cases by Lauson et al.[6] through the respiratory cycle at rest, and by Motley et al.[12] during positive pressure breathing; these measurements indicate that there is, under these conditions at least, a relation between the effective end diastolic filling pressure in the right ventricle and the stroke volume of the ventricle, the stroke volumes changing as much as 25 to 40 per cent for corresponding changes of 2 to 4 mm. Hg in end diastolic pressures. This information is perhaps useful in suggesting that changes in filling pressure in the ventricles need be only very small for considerable increases in stroke volume under certain restricted conditions. How far this can be applied to muscular exercise is unknown.

From the point of view of venous return it is apparent that with the increased cardiac output in exercise, venous blood volumes are shifted so that there is at all times an adequate filling of the central systemic venous reservoir. Heart volume is little if at all increased in normal subjects during moderate

work[13] and even may be decreased, suggesting that the ventricle increases its stroke volume output by increased emptying rather than increased filling.

Starling's law, on the other hand, states that the energy of cardiac contraction, i.e., stroke volume, is proportional to the diastolic *volume* of blood in the ventricular chamber, up to a certain limiting physiologic volume.[2,14] Another relationship, often referred to as Starling's law, that the stroke output increases with increasing diastolic filling *pressure* in the ventricle might better be called Frank's law or principle since Otto Frank's extensive experiments[15] with the frog heart led to this general conclusion.

At all events it would seem, as McMichael and others have noted,[2,16] that the response of the normal heart in moderate exertion does not follow the Starling principle, nor probably the Frank principle either, but operates through other mechanisms, nervous or humoral, tending to increase muscle contractility without increase in fiber length. If there are any increases at all in filling pressure with increased stroke volume, these are very small in magnitude.

When one comes to heavy exertion in normal individuals, however, the situation changes. It has long been recognized that in excessive exercise the heart dilates. Liljestrand, Lysholm and Nylin[13] found that in heavy work the heart size increased an average of 12.7 per cent. But even here, immediately following the exercise with cardiac output still high, heart volume decreased even below control values. Venous pressures in severe exercise are of course impossible to evaluate as indices of effective intracardiac filling pressures due to unknown changes in mean intrathoracic pressures.

From the aforementioned one may suggest as a general proposition that a dilated heart, with incomplete *emptying* during systole, is a heart under strain. Such dilatation may well induce a further increase in stroke volume, in accordance with the Starling principle, but it is apparently a late response in cardiocirculatory effort.

These observations lead to a consideration of actual cardiac failure of various types.

Failure of Normal Heart under Continued Excessive Strain. A direct and uncomplicated example of this situation is traumatic arteriovenous communication in otherwise normal individuals. This condition can be further analyzed by abruptly shutting off and then releasing the arteriovenous shunt. With a large shunt, the essential findings are as follows:[17] There is a marked increase in cardiac output and a progressive development, over months or years, of cardiac hypertrophy and dilatation. Venous and right auricular pressures are at the upper limits of normal or slightly increased; arterial diastolic pressure is low; blood volumes are within normal limits in most early cases but tend to increase in the more severe cases over a period of years.

Upon abrupt closure of the shunt, heart rate slows; arterial diastolic pressure rises; right auricular pressure shows a small but definite decrease in one series reported[17a] and no change in another;[17d] cardiac output is considerably decreased although still above normal. Holman[17c] has reported a sharp rise in both systolic and diastolic arterial pressures and, in cases with large, long-standing communications and cardiac enlargement, a further dilatation of the heart simultaneous with the blood pressure rise.

It is interesting that a further change reported at this time[17a] is an increase in blood volume and in local blood flow in the limbs not involved in the shunt. This suggests a regional redistribution of blood away from the central reservoir coincident with decreased cardiac output. Large arteriovenous communications, untreated over many years, may lead to progressive cardiac dilatation, increased blood volume and marked congestive failure.[17d]

After permanent surgical closure of the shunt rapid diuresis and disappearance of congestive failure occurs; if present, there is also a progressive decrease in heart size to normal over a period of several weeks or longer and a similar gradual return to nor-

mal of the cardiac output. There are obviously various circulatory readjustments in process here.[2]

From the point of view of the development of heart failure the condition presented by a large arteriovenous communication is important in demonstrating how a sustained increase in cardiac output in a perfectly normal heart may lead first to hypertrophy and dilatation and eventually in some instances to frank congestive failure.

Congestive Heart Failure: "High Output" Forms. There has been considerable difference of opinion and some confusion of thought about this general subject which is certainly not surprizing. High output failure includes a variety of very different clinical entities, some of which have not been adequately studied.

Leaving aside the problem of the early stages of development of high output failure about which not much is known as yet and considering only established congestive failure, as for example in severe anemia, one finds the main accepted facts to be that the cardiac output is greatly increased, venous pressures elevated and the congestive state fully established. Blood volumes, as measured by red cell dilution, have been reported as diminished[18a] but by the plasma dye method, which is probably more reliable, they are usually increased.[26]

It may well be that from the point of view of tissue needs this increased cardiac output is still inadequate,[9] but this does not alter the greatly increased burden put upon the heart. Correspondingly, the heart behaves as a heart under strain; the ventricles fail to empty in systole and end diastolic pressures increase although the dilated heart continues to maintain a large output. Whether this state of affairs, before congestion is fully developed, should be called the last stage of "compensation" or the first stage of "congestive failure" is largely academic. As McMichael[2] puts it, "anemic hearts compensated in this manner are, in fact, on the very brink of failure."

The question has in fact been raised whether the congestive state with large cardiac output should be called heart failure[19] at all. To this there is the answer, already mentioned,[9] that the blood flow is still relatively inadequate in these cases, but there is also the much more cogent argument that the congestive state is itself heart failure,[16] a pathologic condition consisting of abnormal intravascular *pressures* rather than deficient intravascular *flow*, but with consequences equally severe—dyspnea, cough, edema, passive congestion of viscera, etc.—all essentially congestive *pressure* phenomena.

Thyroid and beriberi heart disease in congestive failure are similar in mechanics to anemic heart failure. Tissue metabolism in these conditions is greatly disturbed, and the status of the myocardium is also uncertain.

In right-sided congestive heart failure that develops with the pulmonary arterial hypertension of cor pulmonale, high normal or actually increased cardiac output has been found[20,21] but the existence of this condition has also been questioned.[22] Actually the dynamics of pulmonary heart disease are variable and complex[1,23] and patients are encountered with normal or low cardiac output as well as high.

Nonetheless, the high output group constitute a true entity. Marked arterial anoxia is probably important in their causation although there are doubtless other factors. An example, studied recently by Harvey, Ferrer et al.,[24] illustrates a number of features that may be encountered in this category. The data are given in Table 1.

The patient, a middle-aged woman with long-standing bronchial asthma, chronic pulmonary emphysema, cor pulmonale and polycythemia, was admitted to the hospital with extreme obstructive dyspnea and in marked right-sided failure. As shown in Table 1 there was marked arterial anoxia, polycythemia, hypervolemia, pulmonary hypertension, right-sided congestion and a cardiac output nearly twice the normal. Digoxin resulted in a small further increase in cardiac output, rise in pulmonary artery systolic pressure and fall in end diastolic right ventricular pressure (i.e., central

venous pressure)—a typical digoxin response in this type of case. The recovery of this patient, however, following use of bronchodilator drugs and repeated phlebotomy was associated with a drop in cardiac output to normal and marked improvement in arterial oxygen saturation.

TABLE 1

Patient A. D., a female, aged fifty-five.
Diagnosis: Bronchial asthma, pulmonary emphysema, polycythemia, cor pulmonale, congestive heart failure
Residual air—total capacity ratio = 40 per cent

	Arterial O_2 saturation %	Pressures, mm. Hg			Cardiac Output lit./m.	Index	Blood Volume cc./sq. m.		Hematocrit
		Brachial Arterial	Pulmonary Arterial	Right Ventricular			Total	Plasma	
Control	60	160/71	64/29	62/11	10.0	6.1	6060	2040	66
86 minutes after digoxin	61	159/75	75/26	75/4	11.6	7.0			
3 wks. later: fully compensated	79	142/79	30/13	30/2	6.0	3.8	3630	1880	48

To explain this interesting sequence of events it is suggested that the combination of anoxia, polycythemia and hypervolemia was associated with overfilling of the right ventricle, incomplete emptying during systole but a sustained "compensatory" increase in cardiac output, some increase in cardiac emptying with digoxin and decrease in venous congestion. Resolution of the state of congestive failure occurred following relief of anoxia and hypervolemia.

Not all patients, however, respond in this manner. Howarth, McMichael and Sharpey-Schafer[20] report some instances in which intravenous digoxin resulted in a decrease in cardiac output.

Congestive Heart Failure: "Low Output" Forms: Intrinsic Myocardial or Valvular Heart Disease. It has long been known that one of the earliest, if not the earliest, of the manifestations of diminished cardiac reserve is the decrease in maximum oxygen consumption that can be achieved during exercise,[25] and it has been supposed that this is due to a lack of adequate increase in cardiac output, presumably a left ventricular failure. This occurs in cardiac subjects apparently compensated and with no signs of congestive failure.

Additional evidence for this concept was provided by Hickam and Cargill[11a] who found that cardiac patients actually do fail to increase cardiac output in exercise and furthermore that pulmonary arterial pressures increase further during exercise, suggesting additional pulmonary congestion from inadequate left ventricular emptying.

In the course of a progressively diminishing cardiac reserve, in chronic arteriosclerotic or rheumatic heart disease, the point at which resting cardiac output falls below normal probably varies widely from patient to patient; also the point at which frank left-sided congestive failure or right-sided congestive failure makes its appearance is similarly variable. It is certainly true that very low cardiac outputs can exist, especially in the presence of cardiac arrhythmias, in patients at least partially ambulatory with no congestive failure at rest.

Cournand, Ferrer, Harvey and Cathcart[26] have recently studied a series of arteriosclerotic or rheumatic subjects with enlarged hearts, but not in the congestive state. Pressures and cardiac outputs were normal. With digoxin the response was that of a normal heart—decrease in cardiac output and no change in venous pressures. This suggests that the heart volume in these patients at rest was optimal for cardiac performance, i.e., not overdilated. How much of the cardiac enlargement was hypertrophy of cardiac walls and how much enlargement of the cardiac chambers could

not be determined. It is possible that with marked cardiac hypertrophy the physiologic intraventricular volume is larger than with normal-sized cardiac muscular walls.

Left Ventricular Failure. Harvey, Ferrer et al.[24] have reported a series of five cases of left ventricular failure, the patients being treated with intravenous digoxin. The results are consistent and striking—before administration of the drug cardiac output was very low, pulmonary artery pressures increased, right ventricular end diastolic pressures normal, blood volume normal; after digoxin cardiac output increased, pulmonary arterial pressures fell and right ventricular end diastolic pressures did not change. The effect of digoxin was thus apparently a primary action on the left ventricular myocardium, a more complete emptying of this chamber during systole resulting in an increased cardiac output and decreased pulmonary congestion. There was no evidence in these studies of a peripheral venodilator action of digoxin, as suggested by McMichael and Sharpey-Schafer.[27] The data are comparable to some of those reported by Bloomfield et al.[28] on the effects of ouabain, except that the latter caused a rise rather than a fall in pulmonary artery pressures.

These data on left ventricular failure are of interest also from the point of view of salt and water balance and development of edema. They were patients chronically in failure, with very low cardiac outputs, and yet who exhibited no tendency to develop edema as the "forward failure" hypothesis of cardiac edema would demand. Studies of the renal circulation in this type of case are obviously indicated and these are in progress.

Combined Right and Left Ventricular Failure: Action of Digitalis. Two series of cases have been reported, by McMichael and Sharpey-Schafer[27] and Stead, Warren and Brannon.[29]

The measurements of the circulation during decompensation were similar in both series, as were the effects of intravenously administered digoxin or lanatoside C. There was a sharp and rapid drop, within ten to twenty minutes, in a previously elevated right auricular pressure and a large increase in cardiac output taking place within one to two hours. Arterial blood pressure tended to rise, but relatively less than cardiac output, so that the net result was a fall in peripheral resistance. Blood volumes were presumably initially increased in both series although these were not actually measured.

In the studies of Stead et al., following lanatoside C, the same changes also occurred in three patients with severe anemia and increased initial cardiac outputs. The cardiac output increase was found in patients in whom the heart rate showed no significant change as well as in those in whom it was markedly slowed.

McMichael and Sharpey-Schafer noted the similarity of these effects of digoxin to those encountered after venesection, or tourniquets applied to the limbs in patients with congestive failure. They also found that right auricular pressure fell (although only by 1 to 2 cm. saline) in normal subjects given digoxin while at the same time the cardiac output was decreased. The same observations were made in patients with chronic pulmonary disease. They therefore argued that peripheral venous dilatation might be a primary action of digoxin.

The present writer is inclined to hold to a primary myocardial action of digitalis because of the studies of left ventricular failure already mentioned and because of much sound pharmacologic work on the action of digitalis on the heart muscle.

However, whether the response is primary or secondary, the fact remains that with increase in cardiac output associated with digitalization, systemic venous congestion diminishes: there is less blood in the central venous reservoir. As McMichael notes[2] this blood must go somewhere. The amount that could be accounted for by slight arteriolar dilatation is negligible. On clinical grounds it would seem highly unlikely that the extra blood goes to the lungs because one of the earliest manifestations after digoxin is that the patients can breathe much more easily and, of course, pulmonary arterial pressures decrease. The blood must withdraw, so to speak, into some venous depot when the

cardiac output is increased, perhaps into the muscle depots.

The progressive changes, whether of compensation or decompensation, involving blood volume and total tissue fluids, constitute a further problem.

Origin and Development of Systemic Venous Congestion and Edema. Both the "forward failure" hypothesis and the "backward failure" hypothesis of renal dysfunction in congestive heart failure leading to salt and water retention and edema have been presented in considerable detail in the previous papers of this series[2,9,10,14,30] and need not be reviewed again. A few clinical considerations may, however, be mentioned.

The association of a tendency toward fluid retention in subjects with impaired heart action is of course axiomatic. This has been established quantitatively by Stead, Merrill and their collaborators[9,10] in their demonstration of the correlation between decreased renal blood flow and decreased cardiac output. Furthermore, excess body fluid with increased blood volume can by itself induce congestive heart failure. This has been encountered not infrequently in cases of excessive parenteral administration of fluids, for example in postoperative situations. The excess fluid and hypervolemia of water-retention nephritis and the action of desoxycorticosterone probably cause heart failure in large part on these mechanical grounds although arterial hypertension is obviously another factor. The studies of Warren and Stead,[31] in which administration of salt and water to previously compensated cardiac patients with development of edema before any venous pressure elevation occurred, offer further evidence for the forward failure hypothesis of edema formation.

This hypothesis, however, does not appear to be adequate as the sole explanation for fluid retention in congestive heart failure. It does not explain why patients with low cardiac output with strictly left ventricular failure or those with low cardiac output with no congestion do not retain fluid. It does not explain why diuresis may take place in recovery from congestive failure, with no increase in renal blood flow or in glomerular filtration rate.[30]

The venous congestion, or backward failure hypothesis, as a mechanism of fluid retention and edema in congestive heart failure is also valid. That such venous congestion can occur with the failing heart and can be sustained has already been shown. The key to this as a means of water retention has been provided by the experiments of Blake, Wégria, Keating and Ward,[32] showing that increased renal vein pressure above 150 mm. saline results in increased tubular sodium and water reabsorption. This would provide an explanation for salt and water retention secondary to venous congestion.

A clinical study demonstrating a primary rise in venous pressure, with developing failure, is that of Reischman and Grant[33] in which withholding of digitalis from previously compensated patients resulted in rise of venous pressure, presumably from inadequate cardiac emptying, before the appearance of weight gain.

It is, of course, true that high venous pressures can exist, as in constrictive pericarditis and other mechanical obstructive conditions, without development of salt and water retention and general edema.

In the present state of knowledge it would seem, as Bradley and Blake have concluded[30] that both alterations in renal plasma flow and glomerular filtration and alterations in tubular function may operate in the production of cardiac edema. There may well be other factors, too.

Consequences of Congestive Heart Failure on Peripheral Functions, Pulmonary, Visceral, Etc. These have been well covered by Paine and Smith[14] in their review and by McMichael[2] and need no further emphasis.

CONCLUSIONS

Much has been added to the knowledge of congestive heart failure in recent years, particularly through the measurements of renal function and the measurements made possible by cardiac catheterization.

One of the basic phenomena of congestive

heart failure appears to be inadequate ventricular emptying during systole. The Starling principle, whether or not it applies to the normal heart, does apply to the heart approaching and in failure. At an early stage it is probable that increased ventricular dilatation during systole results in an increased systolic output, the cardiac output thus being maintained to satisfy "tissue needs." Even an increased ventricular diastolic pressure (also requiring increased venous pressure) at times may be a favorable compensation, maintaining cardiac output, as in some cases of anemia.

Such compensation, however, eventually becomes excessive, and the overdilated ventricle passes into the end stage in the Starling curve, with decreased stroke volume and decreasing cardiac output.

The argument is presented that the congestive state as such is a form of heart failure, being failure in terms of intravascular and intracardial pressure rather than in terms of blood flow.

The manner of development and maintenance of the congestive state is variously explained. In left ventricular failure it is probably correct to assume simply that pulmonary congestion is caused in the first instance by failure of emptying of the left ventricle accompanied by adequate systolic output by the right ventricle.

In those forms of incipient failure in which salt and water retention occur early, in accordance with the forward failure hypothesis of Stead and Merrill, right-sided congestion develops secondary to increased blood volume. On the other hand, in the cases in which inadequate right ventricular emptying occurs first, with increased diastolic and venous pressures secondary to this, the congestion appears before the hypervolemia. There is still another group in which cardiac output is low and yet no increase in venous pressure or general congestion is found. Just why the congestive state does develop in one group and not in another is not wholly clear. In most instances anything that can be done to prevent blood from accumulating in venous reservoirs under high pressure is of advantage to tissues and circulation alike.

Acknowledgments: The editors have kindly made available to the present writer all of the earlier papers of this series, in advance of their publication. In the discussion here offered a connected and logical presentation of the subject has been attempted, rather than any special critique or review of these earlier papers. The latter, however, have been of great assistance and, as will be apparent, have been generously drawn upon. This assistance is hereby acknowledged.

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Clinico-pathologic Conference

Rheumatic Heart Disease with Respiratory Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, N. M., (B. H. No. 163110), was a sixteen year old, white school girl who entered the emergency room of the Barnes Hospital on September 3, 1948, complaining of shortness of breath, fever and general malaise. The family history was non-contributory. The patient was born with a left spastic hemiplegia, presumably due to birth injury, but considerable function returned on the involved side during her lifetime. She apparently had had no significant illness other than that which ultimately led to her admission; no history of any operations was obtained.

At the age of eight the patient had chorea. The episode lasted about six months, and during the next three years there were several recurrences, each of which appeared during the winter months. At the time of the last bout of chorea the patient was admitted to the St. Louis Children's Hospital where her mother was told that the child had rheumatic heart disease. Following discharge she remained well, except for slight shortness of breath on exertion, until eight months before admission when she developed a chill which was followed by fever and cough. She was seen by a private physician and a diagnosis of "flu" was made. Although the acute episode lasted but a short time, the patient never regained her previous state of good health. Weakness, low grade fever, moderate dyspnea on exertion, intermittent aching of the shoulder and ankle joints without demonstrable signs of inflammation and pain in the muscles occurred to such a degree that the patient was forced to remain home from school. She was confined to bed, however, for only a small portion of the total time that she was ill.

Three months before entry dyspnea increased and the patient was given 0.1 mg. of digoxin daily, with some resultant improvement. Two months prior to admission she developed night sweats, and some weeks later a mild cough productive of a small amount of white mucoid sputum began; concomitantly, the dyspnea grew worse.

Five days before entry the patient had a mild chill, felt feverish, became nauseated and vomited several times. She then apparently felt moderately well until thirty-six hours before entry when she had another chill. Twenty-four hours before admission she became extremely short of breath and complained of rapid pounding of heart. That night she was forced to sit up in bed in order to breathe. Her temperature was 103°F. and she was seen by her physician who prescribed penicillin. She complained of sharp pain in the right chest on deep inspiration, and nausea and vomiting recurred. In addition to digoxin she had apparently received considerable amounts of salicylates until three weeks before her entry to the Barnes Hospital.

At the time of admission her temperature was 39.7°C., pulse 128, respirations 36 and

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blood pressure 110/70. The patient was a thin, pale girl who was mildly orthopneic. Respirations were rapid and shallow. The skin was hot and dry, but no petechiae were seen and there was no apparent cyanosis. A few slightly tender lymph nodes were present in the anterior cervical, axillary and inguinal regions. These measured ½ to 2 cm. in diameter. The pupils reacted normally to light and accommodation and the optic fundi were normal. Examination of the upper respiratory tract showed mild reddening of the pharynx but no other significant findings. Several teeth were carious. The neck veins were not distended and the thyroid gland was not enlarged. Examination of the lungs revealed them to be resonant to percussion. A few moist rales were present at the right base. Examination of the heart revealed that the left border dullness extended 9 cm. to the left of the mid-sternal line in the fifth interspace. The apex beat was strong and diffuse; a thrill was palpable but because of the extremely rapid rate it could not be timed. The rhythm was regular except for an occasional extrasystole. A loud, harsh, grade IV systolic murmur was heard at the apex and was transmitted toward the sternum. It faded, however, toward the base. There was a low pitched rumble at the apex which could not be accurately timed but which was presumed to be diastolic. A blowing grade II systolic murmur was heard over the pulmonic area. The pulmonic second sound was accentuated. The abdomen was soft and flat. The liver edge was felt 1 to 2 cm. below the right costal margin and was somewhat tender. The splenic tip was palpable at the costal margin and was soft but quite tender. No costovertebral angle tenderness was elicited. There was slight weakness and spasticity of the left arm and leg, both of which were smaller than the corresponding extremities on the right. The deep tendon reflexes were hyperactive on the left and a questionable Babinski sign was present on that side. There was no edema or evidence of joint inflammation.

The laboratory findings were as follows: Blood count: red cells, 4,200,000; hemoglobin, 12 Gm. per cent; white cells, 20,800; differential count: stab forms, 19 per cent; segmented forms, 63 per cent; monocytes, 18 per cent. Urinalysis: specific gravity, 1.029; albumin, 3+; sugar, negative; centrifuged sediment, several granular casts, 10 to 15 white cells and 1 to 2 red cells per high power field; acetone, 1+; urine culture, no growth. Stool: not obtained. Blood Kahn test: negative. Blood cultures: negative. Throat culture: non-hemolytic Staphylococcus albus, non-hemolytic streptococci. Blood chemistry: non-protein nitrogen, 36 mg. per cent; total protein, 5.6 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 2.3 Gm. per cent; chloride, 102 mEq./L.; cephalin-cholesterol flocculation test, 1+; thymol turbidity test, 5 units; venous pressure, 150 mm. of saline; circulation time (decholin), 18 seconds. Electrocardiogram: right axis deviation and sinus tachycardia; abnormal T waves suggestive of auricular enlargement.

On admission to the ward the patient was given oxygen by nasal tube, large doses of penicillin and 0.2 mg. of digitoxin daily. On the evening of the first hospital day a distinct diastolic murmur was heard at the mitral area. The patient's condition was unchanged; rales persisted at the right base and distant wheezing with prolonged expiration was audible over both lung fields. The patient did not produce any sputum. On the following morning her temperature was 38°C., pulse rate 90 and respirations 36 per minute. Inspiratory musical rales were heard over the lower half of both lung fields and a few crepitant rales were also present. Dyspnea was mild and the patient seemed considerably improved. Later that day, however, dyspnea increased. Intravenous aminophylline was injected without beneficial effect, and 0.4 mg. of lanatoside C was given intravenously. Oxygen was administered with a positive pressure mask. Several hours later the patient was again distinctly improved and felt apparently quite well for about one hour. Her temper-

ature then rose to 40.5°C., her pulse rate to 152 and respirations to 50 per minute. Moist crepitant rales and coarse ronchi were heard throughout both lung fields. Tourniquets were applied. Her respirations became more rapid and full-blown pulmonary edema developed. She died shortly thereafter.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: I shall ask Dr. Grunow to present the x-ray findings at this time.

DR. OTTO H. W. GRUNOW: A chest film taken on the day after the patient was admitted to the hospital showed that the heart was globular in contour and somewhat enlarged both to the right and to the left. The aortic arch was inconspicuous. The right auricle was prominent. The left border was rather convex and thus consistent with the diagnosis of mitral valvular disease. The hilar shadows were increased in density and there was increased prominence of markings extending into the parenchyma of the lungs, particularly on the right. The soft hazy infiltration was thought to be compatible with an acute infectious process; the costophrenic angles were clear.

DR. ALEXANDER: This case presents a most interesting problem, and we shall attempt to identify the etiology of the febrile illness which led to this child's death. This patient had chorea on at least three separate occasions, and during the third episode was seen at the Children's Hospital at that time her mother was told that the child had rheumatic heart disease. Presumably then, although none of the other signs of acute rheumatic disease such as arthritis or carditis had been manifest, she did develop heart disease by the age of eleven. Dr. Smith, will you discuss the relationship between chorea and rheumatic fever?

DR. JOHN R. SMITH: It has long been known that chorea is the most common manifestation of rheumatic involvement of the central nervous system and not infrequently, as was the case here, chorea may occur in the absence of any other symptoms or signs of acute rheumatic fever. In some children chorea is not followed by any permanent cardiac damage whatsoever. I think there is no question, however, that in many cases rheumatic heart disease develops as a sequel to chorea.

DR. ALEXANDER: It is often stated in the literature that chorea is much less apt to be followed by permanent valvular damage than is acute rheumatic fever with polyarthritis. I take it that you do not agree with that statement, Dr. Smith?

DR. SMITH: No, I do not.

DR. EDWARD MASSIE: I believe, as Dr. Smith does, that chorea is very often followed by rheumatic heart disease, probably almost as often as is classical polyarthritic rheumatic fever. It should be pointed out that chorea is more frequent in females than males, the ratio often being given as approximately three to one.

DR. ALEXANDER: Dr. O'Leary, this patient's last episode of chorea occurred at least five years before her death. Do you believe that any demonstrable lesions will be found in the brain?

DR. JAMES L. O'LEARY: The situation here is rather complicated since the patient had a left spastic hemiplegia at birth. On that basis one would expect a reduction in the size of the right internal capsule, probably some diminution in size of the basal ganglia and, as a matter of fact, the entire right hemisphere may be smaller than the left. I doubt that specific choreic lesions would be present five years after the last bout, but it is conceivable that they might be demonstrated.

DR. ALEXANDER: Are the lesions of chorea specific?

DR. O'LEARY: They are said to be pathologically similar in nature to Aschoff nodules. There is some controversy among neuropathologists, however, as to the specificity of the lesion described in chorea.

DR. ALEXANDER: This patient was apparently well for a number of years before her final illness. Although she became ill approximately eight months before entry,

the acute terminal episode began only a few days before admission and was characterized by high fever and severe respiratory symptoms. Dr. Glaser, how do you interpret her clinical course during the last few months of life?

DR. ROBERT J. GLASER: It seems quite clear that this girl had rheumatic heart disease. Further information in regard to the findings during her last few months of life would be most helpful in enabling us to evaluate her course. For example, if we knew how advanced her cardiac disease was the relative importance of cardiac failure could be better estimated. Many of her symptoms prior to entry were suggestive of congestive failure. I think, however, that this patient probably developed acute rheumatic fever—a not unusual occurrence in such a patient as this one—and furthermore, that she not only had carditis but also rheumatic pulmonary involvement. Although rheumatic pneumonitis is not especially common, it seems to be a well described entity.

DR. ALEXANDER: In other words, you believe that this was a "smoldering" rheumatic process which became acute and severe toward the last few days of her life. Are there any other comments?

DR. THOMAS H. HUNTER: I think that Dr. Glaser's suggestion merits strong consideration, but one of the other possibilities which must be ruled out is that this patient developed subacute bacterial endocarditis eight months before her demise. There are certain features which are compatible with that diagnosis. We are told that she received salicylates for a three-week period, and we also know that she received some penicillin. Although the dosage of salicylates given her is not known, she apparently made no response to them. It is, of course, true that patients with acute rheumatic fever do not always respond to salicylates but, on the other hand, it is conceivable that the lack of response indicated that some other process such as subacute bacterial endocarditis may have been responsible for the illness. The failure to respond well to penicillin does not constitute strong evidence against the diagnosis of subacute bacterial endocarditis since she probably did not receive adequate amounts of the antibiotic. Against the diagnosis, however, is the absence of obvious embolic phenomena, unless the few red cells in the urine are accepted as evidence of embolization. On the other hand, she had definite renal dysfunction as indicated by the elevated non-protein nitrogen; although azotemia may have arisen on another basis, it is well known that long-standing bacterial endocarditis may lead to significant renal damage. Most patients who have had bacterial endocarditis for eight months would have more marked anemia than did this patient.

DR. ALEXANDER: It should be mentioned that the patient's spleen was described as tender; that observation is consistent with the diagnosis of bacterial endocarditis.

DR. GLASER: How many blood cultures were obtained?

DR. ERNEST T. ROUSE: Two were taken and both were negative.

DR. ALEXANDER: Are there other diagnoses to be suggested, or shall we consider only the two proposed by Drs. Glaser and Hunter?

DR. W. BARRY WOOD, JR.: I should like to ask Dr. Grunow if the findings in the chest film were compatible with Lutembacher's syndrome which is characterized by patent foramen ovale and mitral stenosis. It comes to my mind in view of the fact that the x-ray findings suggested a large right auricle and a small aorta. There is no statement as to whether the patient had been fluoroscoped, but fluoroscopy in Lutembacher's syndrome often reveals the so-called "hilar dance."

DR. GRUNOW: We had only a postero-anterior film of the chest, and the findings were entirely in keeping with rheumatic valvular disease. I cannot rule out Lutembacher's syndrome.

DR. ALEXANDER: Dr. Goldman, would you comment on rheumatic pleurisy and rheumatic pneumonitis?

DR. ALFRED GOLDMAN: Rheumatic pleu-

risy is a well accepted manifestation of acute rheumatic fever. I think there is perhaps a bit more controversy in regard to rheumatic pneumonitis since some pathologists apparently are unwilling to accept that diagnosis without qualification. There are many descriptions in the literature of forms of pneumonitis occurring in association with acute rheumatic fever. These vary from lesions in the pulmonary arteries to actual interstitial inflammation in the alveoli. Some of the findings such as edema may be seen in heart failure *per se*, hence the pathologic picture is not always as clearcut as might be desired. I do not believe that Aschoff bodies are actually found frequently in association with acute pneumonitis but they have been described and constitute strong evidence for the entity of rheumatic pneumonia.

DR. WOOD: A recent paper in the Annals of Internal Medicine from the New Haven Hospital described six cases of rheumatic pneumonia which occurred in a series of one hundred patients with acute rheumatic fever.[1] All six of the patients so affected died. The lesions were described in great detail by the pathologists, and I think the most important factor clinically was that the patients all exhibited severe dyspnea and signs of pulmonary involvement without much evidence of congestive heart failure. All had pulmonary involvement at postmortem examination. I think that the case under discussion today is entirely in keeping with this report, and I agree with Dr. Glaser and Dr. Goldman that the patient probably had acute rheumatic pneumonitis.

DR. MASSIE: This girl had at least two chills and perhaps a third one. I think that finding is described in rheumatic pneumonia. In acute rheumatic fever without pulmonary involvement severe chills are certainly uncommon. In the absence of any evidence of pulmonary involvement the chills would be quite suggestive of subacute bacterial endocarditis but in view of the evidence of pneumonia they do not help to differentiate between the two diagnoses.

DR. WOOD: Actually many patients with rheumatic heart disease develop secondary bacterial pneumonia as a complication of congestive heart failure, and it is this fact which makes many pathologists reluctant to recognize rheumatic pneumonia as an entity. The question always arises as to whether the pneumonia is secondary to heart failure or is a manifestation of rheumatic fever *per se*. The pneumonic lesions ascribed to rheumatic fever in the article to which I referred seem convincing; further, Dr. Arnold Rich has shown that experimental lesions very similar to those seen in patients with rheumatic pneumonia may arise on the basis of hypersensitivity.[2]

DR. ALEXANDER: Dr. Massie, what cardiac lesions do you believe will be present?

DR. MASSIE: The answer to your question would be much simpler were this rheumatic heart disease without acute rheumatic fever. It seems likely that the patient had mitral insufficiency and mitral stenosis. It is well known, however, that in acute rheumatic fever with rheumatic carditis, murmurs may appear and disappear in relatively short periods of time; thus the presence of a murmur during acute rheumatic carditis does not necessarily indicate significant permanent valvular damage. Nonetheless, I think that this patient will have mitral stenosis and insufficiency.

DR. ALEXANDER: Do you believe that the patient had cardiac failure?

DR. MASSIE: I am not at all sure that she did; as a matter of fact I favor rheumatic carditis, without failure, and rheumatic pneumonitis as the explanation of the final illness.

DR. ALEXANDER: This patient had marked dyspnea on the night before she came into the hospital and had had some before that. Yet at no time did she have cyanosis or

[1] SELDIN, D. W., KAPLAN, H. S. and BUNTING, H. Rheumatic pneumonia. *Ann. Int. Med.*, 26: 496, 1947.

[2] RICH, ARNOLD R. and GREGORY, JOHN E. Experimental anaphylactic lesions of the coronary arteries of the "sclerotic" type, commonly associated with rheumatic fever and disseminated lupus erythematosus. *Bull. Johns Hopkins Hosp.*, 81: 312, 1947.

edema and the circulation time and venous pressure were normal. The neck veins were not distended. On the basis of those findings it is rather difficult to make a diagnosis of heart failure, and acute rheumatic carditis may well explain most of her signs and symptoms. If this patient had had rheumatic carditis without pneumonitis, what would you have said of her prognosis, Dr. Massie?

DR. MASSIE: The prognosis of acute fulminating rheumatic fever is bad, particularly when there is marked evidence of carditis. I must repeat that I was impressed by the fact that she had several chills for they suggest to me pulmonary involvement. At the House of the Good Samaritan in Boston I saw a number of young children die with fulminating acute rheumatic fever. Many of these children had very impressive cardiac findings and high fever but no evidence of bacterial invasion of the lungs or blood stream.

DR. GLASER: Even if this patient did have some degree of heart failure her lack of response to the usual measures would have been quite characteristic of a patient with acute rheumatic carditis for it is well known that such patients do not respond to the therapeutic agents which are very effective in heart failure due to uncomplicated rheumatic heart disease.

DR. ALEXANDER: Are patients in this age group likely to die of acute carditis if they do not have severe underlying valvular disease?

DR. MASSIE: The presence of chronic valvular disease has a deleterious influence in the prognosis of acute carditis. I doubt, however, that this girl had severe mitral stenosis.

DR. WOOD: In the cases which were reported from New Haven all of the patients with rheumatic pneumonitis also had acute rheumatic carditis and almost all of them terminally had some degree of heart failure. Apparently the combination of myocardial and pulmonary involvement led to a fatal outcome.

DR. AXEL R. GRONAU: How frequently does one see acute, severe rheumatic carditis without abnormalities in the electrocardiogram?

DR. MASSIE: I believe the tracing in this case was definitely abnormal in that the T waves were very high and broad, suggesting auricular wall involvement. There was also marked right axis deviation. Some right axis deviation is not unusual at the age of sixteen but in this patient the degree was rather marked. Dr. Gronau probably was more interested in conduction defects, but none was seen here.

DR. CARL G. HARFORD: Did this patient receive penicillin after her admission?

DR. ROUSE: Two blood cultures were taken as soon as she reached the ward, and then penicillin therapy was begun in large dosage.

DR. ALEXANDER: In summary, I believe that we feel that this patient had acute rheumatic fever with acute carditis and probably acute rheumatic pneumonitis as well. Further, she had rheumatic heart disease with mitral stenosis and insufficiency, and she may have had subacute bacterial endocarditis.

DR. WOOD: Dr. Alexander, do you think that this patient had subacute bacterial endocarditis?

DR. ALEXANDER: No, I do not. Do you still think so, Dr. Hunter?

DR. HUNTER: No, I do not really think so, but I don't see how it can be definitely ruled out.

Clinical Diagnoses: Acute rheumatic fever with carditis and pneumonitis; ? subacute bacterial endocarditis.

PATHOLOGIC DISCUSSION

DR. CLARENCE PICKARD: When the chest was opened, the pericardial sac was found to contain 40 cc. of clear yellow fluid. The heart was enlarged, weighing 340 Gm. in contrast to the 180 to 200 Gm. which would be normal for the body weight of this patient. Dilatation and hypertrophy were especially advanced in the right ventricle and in the left atrium. The myocardium of the right ventricle measured 6 mm. in thickness. On the surface of the right atrium

there was a deposit of fibrin 5 cm. in diameter. There was fibrous thickening of the endocardium of the left atrium, the mitral valve and the endocardium of the left ventricle. The tricuspid valve was thickened moderately and on the free edge of one of its leaflets there was a clump of light tan, translucent verrucae ½ to 2 mm. in diameter. The endocardium of the right atrium was slightly thickened. The mitral valve was thickened and fibrotic, and the normal indentations of the commissures of the leaflets were moderately obliterated by fibrous scar tissue. Although the ring measured 75 mm. in circumference, the opening through the valve leaflets was much smaller. A few small fresh verrucae were present on the edges of the mitral valve leaflets. The aortic and pulmonic valves were normal. The myocardium, aside from the hypertrophy, appeared grossly normal.

There were 200 cc. of clear yellow fluid in each pleural space, and a few fibrous adhesions were noted over the upper and lower lobes of the right lung. Small deposits of fibrin were present on the pleural surfaces of each lobe. The lungs were large, firm and of a uniform, rubbery consistency. From their cut surfaces red foamy fluid oozed but there was no profuse bleeding. No focus of bronchopneumonia was apparent.

The other viscera examined were not grossly remarkable.

DR. GUSTAVE J. DAMMIN: From the gross findings several diagnoses were made. The first was that of rheumatic heart disease as evidenced by chronic endocarditis involving the mitral valve with a moderate degree of stenosis. In addition, there were several verrucae on the mitral valve as well as on the tricuspid valve; these indicated an acute, or at least a subacute, rheumatic process. There was fibrinous pericarditis, enlargement of the heart and widespread endocardial thickening, all of which afforded further evidence of chronic and acute involvement of the heart by rheumatic fever.

The second diagnosis concerned the pulmonary involvement. The lungs exhibited the manifestations of pulmonary edema, but the gross appearance of the lungs was sufficiently different from that of ordinary pulmonary edema to suggest that this was an instance of rheumatic pneumonia, and that diagnosis was made on the basis of the gross specimen. It is difficult to define the gross characteristics of rheumatic pneumonitis and to differentiate it from the changes of subacute passive congestion. In this specimen the interstitial tissue was thickened, there was some fluid in the alveoli and the light color was more suggestive of pneumonia than is the darker color which one associates with chronic passive congestion. There also was fibrinous pleurisy and in each pleural cavity fluid was present.

The first section (Fig. 1) is from the myocardium at the base of the left ventricle and shows an Aschoff nodule which has the fusiform shape associated with such nodules at the end of one or two months. Some of the cells within the nodule have very dense nucleoli and can be identified as Anitschkow cells. An outstanding and characteristic feature of these cells is the basophilic, rod-shaped nucleus which extends the entire length of the cell; the Anitschkow myocyte is the reticulum cell of the myocardium. It is believed by many that Anitschkow cells are the precursers of the Aschoff cells which form rheumatic nodules in the myocardium.

Figure 2 is a photograph of a portion of the tricuspid valve. There is prominent vegetation, the outer surface of which is composed entirely of fibrin; a few fibroblasts are present at the base of the vegetation. These features constitute evidence of acute verrucous endocarditis of rheumatic origin. Just beneath the vegetation the valve structure is acellular and fibrous, indicating a chronic inflammatory process in the valve. In the base of the mitral valve (Fig. 3) there is an abnormal number of large vessels which indicate previous inflammatory involvement; the valve has been thickened by a large amount of hyalinized collagen.

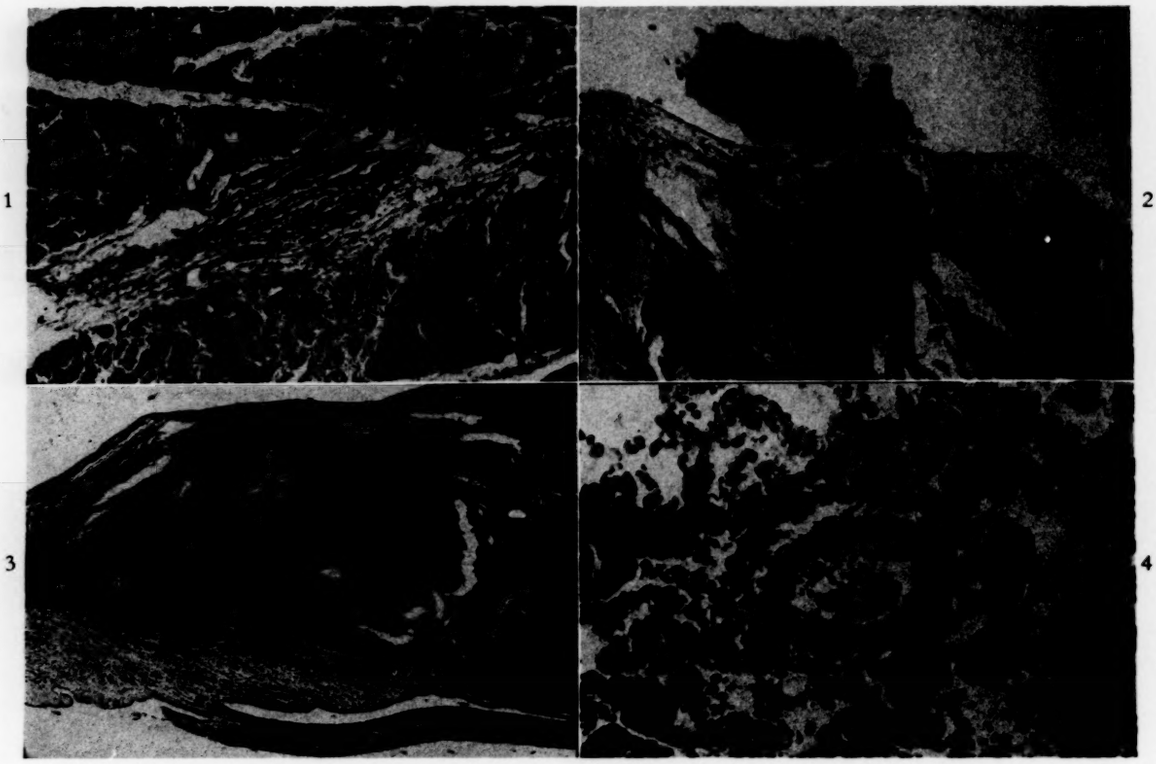

FIG. 1. Aschoff nodule of one to two months in age in the myocardium at the base of the left ventricle.
FIG. 2. Acute verruca on the scarred leaflet of the tricuspid valve.
FIG. 3. Dense collagenous scarring and thickening of a leaflet of the mitral valve with prominent vascularization, particularly on the right side of the field.
FIG. 4. Intimal thickening of rheumatic arteritis in a small pulmonary vessel.

In sections of the lungs there were anatomic changes, the appearance of which did not permit exact separation on an etiologic basis. Some of the smaller arteries of the lungs were thickened, primarily in the media, as occurs in pulmonary hypertension. Other vessels showed the change illustrated in Figure 4—proliferation of the intima without change in the media. This change is one of the more characteristic ones found when there is rheumatic involvement of the arteries, regardless of their location. It has been described in the vessels of the liver, pancreas, heart and lungs. In this section macrophages are also seen. Although it is not apparent in the photomicrograph many of the macrophages contain large amounts of hemosiderin, evidence of some degree of chronic passive congestion. There is also some interstitial thickening and increased cellularity of the alveolar walls. These features are more apparent in a less highly magnified photomicrograph of the lung (Fig. 5) where there is shown infiltration of both polymorphonuclear and mononuclear cells in the alveolar walls; fibrin is also seen in and along the walls of some of the alveoli. In the fibrin there are a few polymorphonuclear leukocytes. These findings are indicative of rheumatic pneumonia. We did not find the great number of hyaline thrombi which are commonly associated with rheumatic pneumonia, nor did we see any foci in the alveolar walls of specific fibrinoid nodules which are described in this disease. There were, however, many hemorrhages into the alveoli, a common finding in rheumatic pneumonia. The total picture was interpreted as representing the changes of both chronic passive congestion and of acute rheumatic pneumonitis.

Microscopic examination of the liver revealed a lesion which was entirely un-

5 6

FIG. 5. Thickened and infiltrated alveolar walls and precipitated protein, fibrin and macrophages within the alveoli. The varied character of these changes indicates the combined effect of both congestion and rheumatic pneumonitis.

FIG. 6. Section of the liver showing mid- one necrosis.

expected from the gross appearance of the organ. In almost every hepatic lobule there was an area of necrosis, most often found in the mid-zone of the lobule. This finding is illustrated in Figure 6. Such necrosis is not the type that occurs usually with acute passive congestion for it was removed from the portal and central veins. In fact, the congestion of the abdominal viscera was minimal. There are few references to changes in the liver in rheumatic fever. In May Wilson's monograph on rheumatic fever, however, she refers to similar mid-zone necrosis which she noted in a very few of her cases.[3]

To summarize our findings then, there were the manifestations of chronic rheumatic endocarditis with involvement of the endocardium and the myocardium, and of acute rheumatic carditis with involvement of the valves, the presence of Aschoff nodules in the myocardium and the presence of fibrinous exudate and fluid in the pleural cavities.

There definitely were two distinct processes in the lungs, and the degree to which each change contributed to the final picture cannot be accurately determined. Chronic passive congestion of the lungs was present although the terminal heart failure was primarily that of the left heart; there was no fluid in the peritoneal cavity nor did any of the abdominal viscera show a significant degree of passive congestion. The passive congestion in the lungs was probably of short duration, but there was also pneumonitis characterized by the presence of fibrin in the alveoli and interstitial infiltration of the alveolar walls by mononuclear and polynuclear cells. The vessels in the lungs showed changes which were compatible both with pulmonary hypertension of some standing and with rheumatic arteritis. Actually the rheumatic arteritis was healed for the change was primarily that of intimal thickening in the smaller arteries.

The changes in the liver were rather unusual; as indicated there is only one reference in the literature to such changes. It is interesting that the thymol turbidity and the cephalin-cholesterol tests were normal.

The brain was not examined.

Anatomic Diagnoses: Chronic endocarditis of the mitral valve with moderate stenosis; acute verrucous endocarditis of the mitral and tricuspid valves; chronic and subacute rheumatic myocarditis; chronic passive congestion and edema of the lungs, moderate; acute interstitial pneumonitis involving all lobes of the lungs; focal necroses in the liver, primarily mid-zonal.

[3] WILSON, M. G. Rheumatic Fever. New York, 1940. Commonwealth Fund.

Case Reports

Gastric Alkalosis with Hypokalemia*

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ALKALOSIS caused either by loss of gastrointestinal secretions or by excessive intake of alkali occurs frequently and the outstanding clinical and laboratory features of the syndrome have been thoroughly described.[1–18] Within the last few years reduction of the serum potassium concentration has been observed as an occasional feature of alkalosis in some cases due to Cushing's syndrome,[19,20] congenital alkalosis with diarrhea[21] and gastric alkalosis.[22,23] In most of these instances the electrolyte composition of serum is abnormal in that the (K^+) and (Cl^-) are reduced while the (HCO_3^-) is elevated.

The major portion of the potassium content of the body is contained not in the extracellular but in the intracellular fluid, about 70 per cent of which is muscle fluid. In each of the aforementioned clinical syndromes evidence indicating loss of intracellular potassium has been presented. Muscle cells in one case of Cushing's syndrome with alkalosis[24] and in two cases of gastric alkalosis[23] have been shown to contain abnormally low concentrations of potassium and abnormally high concentrations of sodium. Balance studies[20,21,23,25,26] have indicated that in the intracellular fluid (K^+) was low and that potassium was replaced by sodium.

Potassium depletion in the rat, produced experimentally by low potassium diets (cf. congenital alkalosis with diarrhea and gastric alkalosis) and/or administration of large doses of desoxycorticosterone acetate (cf. Cushing's syndrome), has resulted in the development of an electrolyte disturbance characterized by alkalosis, elevation of serum (HCO_3^-), reduction of serum and muscle (K^+) and elevation of muscle (Na^+).[27]

The therapeutic implications of these disturbances in electrolye composition of body fluids are important. In congenital alkalosis with diarrhea[28] and in Cushing's syndrome with hypokalemia and alkalosis[19,20] use of potassium salts has been shown to be beneficial. The observation has been made that repair of the disturbance is not possible by administration of sodium or ammonium salts unless potassium salts are also employed.

The case herein reported is one of gastric alkalosis in an adult with evidence of potassium deficiency treated successfully with potassium chloride in addition to sodium and ammonium chloride.

CASE REPORT

A forty-nine year old white male cabinet worker was admitted to this hospital with the chief complaints of weakness, anorexia, diarrhea, weight loss and swelling of the extremities. Fourteen years before admission a posterior gastroenterostomy had been performed for epigastric pain. He was asymptomatic thereafter until seven months before admission when the symptoms which brought him to the hospital appeared and became progressively worse. Work-up revealed clinical and laboratory evidence of malnutrition; a gastrojejunocolic fistula was demonstrated roentgenographically. Every effort was made to improve the patient's nutritional status preoperatively. His diarrhea

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was brought under control and he regained 15 of the 45 pounds which he had lost. Three months after admission the fistulous tract was excised *en bloc*, intestinal continuity was reestablished and a temporary cecostomy was done. Postoperatively there was only moderate drainage (about 250 cc. per day) from the cecostomy tube. However, drainage from the intragastric suction ranged from 2 to 5 liters per day. (Table I.) Parenteral replacement therapy is listed in Table I. Apathy and drowsiness appeared and increased progressively from the second postoperative day, and by the sixth day most of the classical clinical and laboratory signs of alkalosis were present.

TABLE I

SUMMARY OF AVAILABLE DATA ON FLUID AND ELECTROLYTE BALANCE DURING IMMEDIATE POSTOPERATIVE PERIOD

Post-operative Day	Intake			Output	
	Parenteral Fluids cc./day*	Oral Fluids cc./day†	Sodium Chloride mEq./day	Wangensteen Drainage cc./day	Urine cc./day
0	3,000	.....	350	2,400	Unrecorded
1	4,000	.....	170	3,000	Unrecorded
2	6,500	.....	380	4,000	1,125
3	5,000	.....	340	4,800	900
4	3,000	1,260	280	4,200	550
5	4,000	4,500	415	2,100	1,100
6	6,000	2,060	555	.....	2,050
7	2,000	3,560	280	.....	1,850
8	.....	3,600	150	.....	1,900

* Includes whole blood, plasma, saline, dextrose in saline, dextrose in distilled water and amigen.

† Includes milk, fruit juice and water.

Chemical determinations reported herein were performed by methods conventionally used in the study of acid-base disturbances. Heparinized arterial blood was collected and handled anaerobically for all determinations. Values for (HCO_3^-) were calculated from the measured pH and total CO_2 content. Sodium and potassium were determined flame-photometrically. Concentration of sodium (or potassium) per liter of erythrocytes, $(Na^+)_c$ was calculated from whole blood, $(Na^+)_{w.b.}$ and plasma $(Na^+)_p$ sodium concentrations by the formula:

$$(Na^+)_c = \frac{(Na^+)_{w.b.} - (Na^+)_p(1\text{—Hematocrit})}{\text{Hematocrit}}$$

As can be seen from Table II the alkalosis initially was very severe and associated with high plasma (HCO_3^-) and low plasma (K^+). There was a striking deficit in erythrocyte (K^+) counterbalanced by an increased (Na^+). The P_{CO_2} calculated from the data was 60 mm. Hg, quite in keeping with the patient's slow, shallow respiration. Electrocardiogram showed a prolonged Q-T interval. Renal function studies performed at the height of the alkalosis (Table III) showed reduction in filtration rate. Despite this and the reduction of plasma (K^+) the excretion rate of (K^+) was high (about 50 mEq./day). Notwithstanding the severe alkalosis and greatly elevated plasma (HCO_3^-), the urine was unequivocally acid.

When the nature and extent of the disturbance of the electrolyte structure of the patient's body fluids was appreciated, intragastric suction was discontinued. Therapy with intravenous potassium chloride was started. The first 7.5 Gm. induced only a slight but significant rise in the plasma (K^+), associated clinically with improvement in the patient's state of consciousness. In the next thirty-six hours the patient received 10 Gm. of potassium chloride orally and 24 Gm. of ammonium chloride. On this regimen there was prompt clinical improvement and rapid reversion of the laboratory findings to normal. (Table II.) Physiologically correct concentrations of potassium and bicarbonate in plasma and of potassium and sodium in erythrocytes were restored seventy-two hours after the beginning of therapy. The patient's subsequent course, without further therapy, was uneventful.

COMMENTS

Depletion of the total body K^+, a feature of gastric alkalosis which has heretofore not been emphasized in the adult, was assumed to exist in this case on the basis of low plasma and erythrocyte (K^+). Darrow[27] has shown that in the rat a reciprocal relationship exists between the (Na^+) and (K^+) of muscle cells and that the latter varies inversely with the serum (HCO_3^-). While the data on erythrocyte cation composition, as computed by difference, are liable to large errors and are less useful than when in terms of concentration in cell water, the conclusion is probably valid that erythrocyte K^+ had been replaced by Na^+ at the height of the alkalosis. When the (HCO_3^-) returned to normal, the erythrocyte (K^+) was restored. The relationship, therefore, between erythrocyte (Na^+) and (K^+) and

plasma (HCO_3^-) in this patient was comparable to that observed by Darrow in rat muscle and serum.

The depletion of body potassium in an individual whose intake was essentially zero probably resulted from a combination of severe metabolic alkalosis has been reported previously.[31] We have not remeasured this patient's inulin clearance. However, the variation in blood urea nitrogen levels rising from normal preoperatively to 45 mg. per cent on the fifth postoperative day, to

TABLE II

SUMMARY OF DATA ON BLOOD ELECTROLYTE COMPOSITION *

Post-operative		Plasma							Erythrocyte †	
Day	Time	pH	Na^+ mEq./L.	K^+ mEq./L.	Cl^- mEq./L.	Total CO_2 mM./L.	HCO_3^- mEq./L.	Hematocrit Per Cent	Na^+ mEq./L.	K^+ mEq./L.
6	9 P.M.	7.59	138	1.71	68	56.6	54.8	40	45	69
7	10 A.M.	7.55	138	2.04	...	56.1	54.1			
8	10 A.M.	....	136	3.46	94	34.1				
10	10 A.M.	7.46	137	3.67	100	27.1	25.9	40	5	96

* Between 1 A.M. and 10 A.M. on the seventh postoperative day the patient received 7.5 Gm. of KCl parenterally.
† Expressed as per liter of erythrocytes.

TABLE III

SUMMARY OF RENAL FUNCTION STUDIES

Total Concurrent Time	Plasma K^+	Urine Flow	Inulin Clearance	Excreted			Urine pH
				K^+	NH_4^+	Titratable Acid	
Minutes	mEq./L.	ml./min.	ml./min.	μEq./min.	μEq./min.	μEq./min.	
−60	Infusion started containing NaCl 143 mEq./L. at 6 ml./min.						
0–17	1.80	2.00	75	39	34	15	5.90
17–39	1.82	2.00	78	36	34	16	6.09
39–56*	1.78	1.71	66	26	35	15	6.00
56	Infusion changed to NaCl 130 mEq./L. KCL 50 mEq./L. at 6 ml./min.						
121–142	2.01	1.57	76	27	35	14	6.14
142–163*	2.09	1.43	66	19	28	13	6.10

* The data suggest that urine collections in these two periods were incomplete.

loss of gastrointestinal secretions (containing an average of 7 mEq. /L. of K^+)* and failure of the kidney to retain this ion in the face of severe depletion. The long antecedent period of diarrhea may have been a contributing factor as in the sprue syndrome.[29,30]

The inulin clearance was somewhat low. Temporary depression of filtration rate in 55 mg. per cent on the sixth and back to 28 mg. per cent on the seventh suggests that the observed azotemia was attributable, in part, to an acute depression of filtration rate.

More serious renal damage manifested by prolonged elevation of the blood urea nitrogen, hypertension, marked oliguria or anuria, hematuria, proteinuria and cylindruria have been frequently reported in association with the metabolic alkalosis induced by loss of gastrointestinal secretions

* While this figure represents an average from the literature, it is noteworthy that gastric secretions have concentrations of K^+ averaging about 20 mEq./L. and ranging up to 30 mEq./L.[48–50]

or by excessive intake of alkalies.[1-5,9-18,-32-35] While in some instances pre-existing renal damage was known to have been present, in others renal function was quite normal before the episode of alkalosis. The damage usually proved reversible. In those patients who succumbed during alkalosis histopathologic examination revealed lesions which were located predominantly in the tubular epithelium.[2,11,33,37] The latest available necropsy protocol points out that the lesion is situated in the ascending portion of the distal convoluted tubule and bears a striking similarity to the picture occurring in the "crush" syndrome ("lower nephron nephrosis").[38]

The excretion of an acid urine by a patient with severe alkalosis is surprising. This observation has been made and commented upon in previous reports.[3,16,26,34,39] It has been noted in dogs[40] and in normal men[40a] that in alkalosis induced by administration of sodium bicarbonate the urine pH became alkaline whenever the plasma (HCO_3^-) exceeded 25 mM./L. While no measurements of urinary CO_2 content were made in this patient, no more than a trace could have been present at the observed urinary pH. Yet this patient's plasma (HCO_3^-) was in excess of 50 mM./L. Patients with nephritis require more alkali and higher plasma (HCO_3^-) to achieve an alkaline urine.[41-44] The electrocardiograms taken showed no abnormalities except prolongation of the Q-T interval. Such prolongation is frequently observed in hypokalemia.[45]

From a therapeutic standpoint it seems obvious that potassium salts should be administered to adults with alkalosis when potassium depletion is also present. If oral administration is impractical, they may be given intravenously (in concentrations under 75 mEq./L. to avoid local pain) or by hypodermoclysis. The electrocardiogram is a valuable tool to indicate impending toxicity from overmedication with potassium salts due to its distinctive pattern in hyperkalemia. Several recent papers have reviewed the distinctive electrocardiographic patterns.[45-47]

SUMMARY AND CONCLUSIONS

A case of severe metabolic alkalosis is presented. Unusual findings to which attention is called include a reduction of plasma (K^+); reduction of (K^+) and elevation of (Na^+) of erythrocytes; urinary pH of 6.0 when the blood pH was 7.59, and reduction of glomerular filtration rate (inulin clearance). Therapy with potassium and ammonium chloride was followed by prompt clinical improvement and by rapid restoration to a normal plasma and erythrocyte electrolyte pattern.

Acknowledgment: The authors gratefully acknowledge the helpful advice and criticism given them by Dr. Robert W. Berliner.

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Cardiopulmonary Function Studies in a Patient with Ligation of the Left Pulmonary Artery*

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LIGATION of a right or left pulmonary artery has been performed many times and it is well known that the involved lung does not become fibrotic or gangrenous as long as the bronchial artery is left intact.[1–3] However, no report of physiologic studies under these circumstances has appeared until recently when Janton et al.[4] published the results of bronchospirometric observations in a patient who had been subjected to a ligation of the pulmonary artery. The present report is concerned with similar but more extensive observations, including studies of cardiac function in a patient following ligation of the main left pulmonary artery.

CASE REPORT

A twenty-three year old Italian-American girl entered the Presbyterian Hospital in 1945, with the typical history, physical signs and laboratory findings of a Streptococcus viridans subacute endarteritis superimposed on a patent ductus arteriosus. Significant points in her past were history of a heart murmur, moderate physical limitation in a cardiac class during school years and inability to obtain a job because of the murmur. Her hospital course was complicated by bilateral pulmonary infarcts. No peripheral emboli were detected. Immediately following sterilization of her blood stream with parenteral penicillin, the patent ductus arteriosus was ligated but not severed.

Five months after a smooth postoperative recovery and discharge from the hospital, recurrence of the machinery murmur which had disappeared following operation was noted. At this time several blood cultures revealed Staphylococcus citreus, and the patient was readmitted to the hospital. Chest x-ray at this time disclosed enlargement of the left heart, dilatation of the pulmonary artery and increased vascular markings. (Fig. 1.) A pulmonary infarct in the left lower lobe was the only embolic phenomenon noted. After adequate penicillin therapy she underwent re-exploration. At operation an aneurysm communicating with both the aorta and the pulmonary artery was found at the site of the ductus arteriosus. In dissecting the aneurysm free from its attachment to the left pulmonary artery a tear occurred at the juncture of these two structures making it necessary to clamp and tie off the artery in order to control hemorrhage. The aneurysm was removed and the defects in the aorta and pulmonary artery were closed. The postoperative course was complicated by a left pleural effusion which subsided after a single thoracentesis, and by mild cardiac decompensation which responded well to digitalis.

At the present time, two years after the second operation, the patient is feeling well, has a normal exercise tolerance, and holds a full-time job as a sewing machine operator. Physical examination is entirely normal aside from a faint systolic murmur in the pulmonic area and a 4 cm. elevation of the left diaphragm. Fluoroscopic examination of her chest is essentially normal except for limited motion of the high left diaphragm. Chest x-ray (Fig. 2) shows con-

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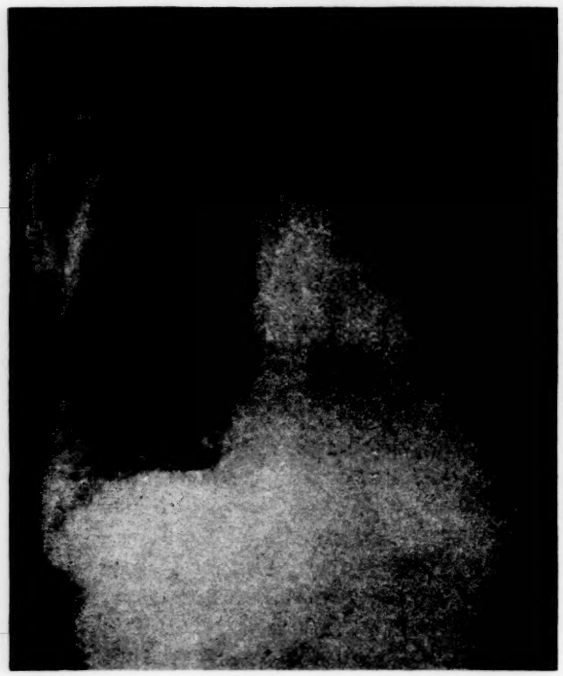

FIG. 1. X-ray taken before the second operation.

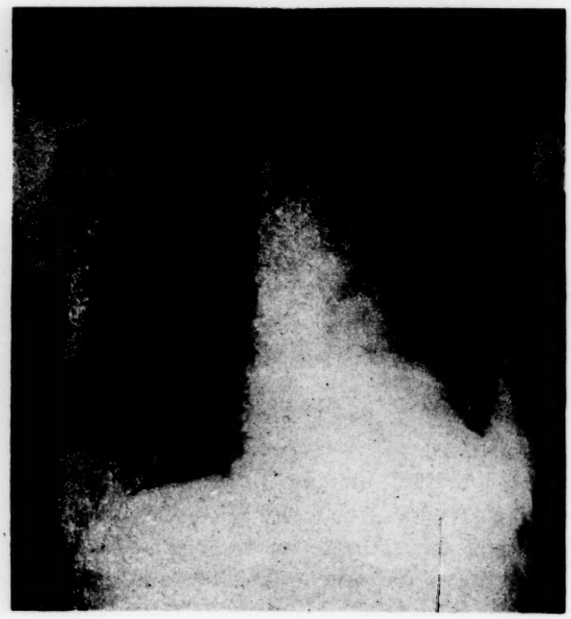

FIG. 2. X-ray taken two years postoperatively at the time of the physiologic studies.

siderable decrease in the size of the cardiac silhouette and in the prominence of the vascular markings in comparison with her preoperative film.

METHODS OF STUDY

Pulmonary function was studied by the methods previously described.[5] Vital capacity and maximum breathing capacity were measured on a recording spirometer, the residual air and the index of intrapulmonary mixing by the open circuit method. Pulmonary ventilation, pulmonary gas exchange and arterial oxygen saturation were determined during rest and the standard exercise test. The separate function of each lung was studied simultaneously by means of the Zavod catheter.[6] Spirometric tracings were recorded and three-minute samples of expired air for measurement of minute ventilation and gas analysis were collected concurrently from both the right and left lungs.

Pressures were measured in the pulmonary artery and the chambers of the right heart by means of Hamilton manometers. The direct Fick method was employed to measure cardiac output.[7]

RESULTS

Results of the pulmonary function study (Table I) were within normal limits, except for hyperventilation and therefore a diminished rate of oxygen removal, under all conditions of observation. As may be seen from Table II and spirographic tracings (Fig. 3) obtained from each lung during bronchospirometry, the left lung, although normally ventilated, consumed a negligible amount of oxygen. In addition there was a slight reduction of the vital capacity of the left lung. The carbon dioxide output was diminished to a lesser degree than oxygen consumption as determined by direct analyses of the expired air. When this lung was ventilated by pure nitrogen, no change was noted in the arterial oxygen saturation, which remained 94 per cent. Cardiocirculatory studies (Table III) showed normal pressures in the pulmonary artery and chambers of the right heart. The cardiac index was high.

COMMENT

While pulmonary function studies were essentially within predicted limits, bronchospirometry revealed strikingly abnormal findings. The left lung, which has no

pulmonary arterial blood supply, is normally ventilated but participates only slightly in pulmonary gas exchange. The studies of Janton et al.[4] in a similar case showed a diminished gas exchange in the affected left lung. They collected several pairs of gas samples from the lungs functionally separated at the end of forced expirations. The samples from the left lung contained an average of 19.14 per cent of oxygen and 3.74 per cent of carbon dioxide. Since their catheter was sealed in place only during actual sampling, they postulated mixing of right and left lung air between periods of gas collection as the explanation for the observed difference between the gas content of the left lung samples and that of room air. They assumed that bronchial artery anastomoses with the pulmonary capillary bed could account for the oxygen and carbon dioxide values on the left side but found no available evidence to support this assumption.

TABLE I
RESULTS OF PULMONARY FUNCTION STUDIES

	Normal	Observed
I. Lung volumes in cc.		
Vital capacity	2975	2595
Residual air	745	620
Total capacity	3720	3215
Residual air/total capacity × 100	20	19
II. Maximum breathing capacity in L./min	85	83
Ventilation in L./min./body surface m^2		
Rest	3.2 ± 0.4	4.3
Exercise	9.0 ± 1.7	13.0
Recovery first minute	10.9 ± 1.5	15.6
Recovery fifth minute	4.9 ± 0.6	5.9
Length of dyspnea in minutes	0 − 1	1
III. Index of intrapulmonary mixing (alveolar nitrogen per cent after 7 minutes oxygen breathing)	<2.5	1.4
Arterial blood		
Oxyhemoglobin saturation per cent rest	96 ± 2	96.3
Oxyhemoglobin saturation per cent recovery first minute	96 ± 2	92.8
IV. Oxygen consumption in cc./min./body surface m^2		
Rest	126 ± 2	141
Standard exercise	463 ± 76	526
Rate of oxygen removal in cc./L. of ventilation		
Rest	45.1 ± 4.3	37.0
Standard exercise	60.2 ± 9.5	46.0

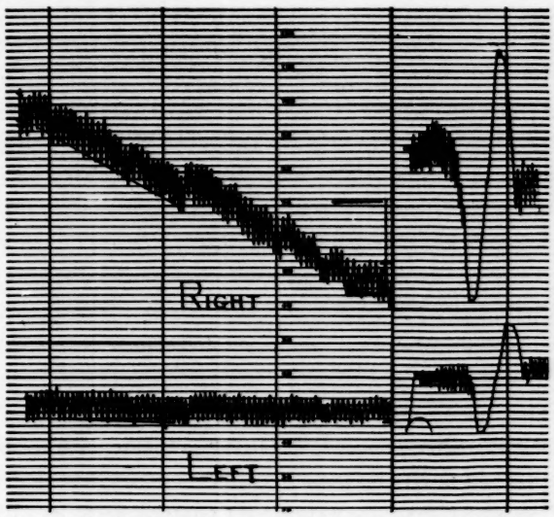

FIG. 3. Spirographic tracings of each lung. The vital capacity determination is to the right, the oxygen consumption and ventilation to the left.

In our studies the tip of the bronchial catheter was sealed in the left main bronchus throughout the procedure, eliminating mixing of air between the two lungs as the source of appreciable carbon dioxide output. Thus bronchial artery anastomoses with the pulmonary capillary bed could be shown to provide a reasonable explanation for the gas exchange observed in the left lung. This hypothesis most readily explains the fact that carbon dioxide output is greater than oxygen consumption. Since, as is well known, the carbon dioxide dissociation curve becomes steeper as the carbon dioxide tension becomes lower, a small gradient in carbon dioxide tension between the alveoli and pulmonary capillaries will result in a relatively large change in carbon dioxide volume. Consequently, even though the left lung was perfused entirely with arterial blood, an appreciable carbon dioxide output was observed. On the other hand, it is difficult for arterial blood to take up additional oxygen since the oxygen dissociation curve becomes flatter as higher

oxygen tensions are reached, requiring a high alveolocapillary gradient to add a small increment of oxygen to blood which is already almost fully saturated.

Simple diffusion through bronchiole walls is an alternative explanation for gas exchange in the left lung. Since carbon dioxide diffuses much more readily through tissues than oxygen, a disproportion in carbon dioxide and oxygen exchange would be anticipated. However, it seems highly unlikely that the latter mechanism could account for the relatively large amount of gas exchange observed in this patient.

TABLE II
RESULTS OF BRONCHOSPIROMETRY

	Left Lung Per Cent of Total Function	
	Normal	Observed
Ventilation	35–50	37
Vital capacity	35–50	30
Oxygen intake	35–50	6
Carbon dioxide output	35–50	24

The only abnormality observed in the pulmonary function study was hyperventilation associated with a decreased rate of oxygen removal at rest, during exercise and in the postexercise recovery period. In this respect our patient resembles a group of patients who had large air cysts which were poorly perfused with blood, yet were well ventilated by virtue of free communication with the tracheobronchial tree.[8]

SUMMARY

A case is reported in which cardiopulmonary function studies were performed on a patient two years after the left pulmonary artery was ligated. Cardiac catheterization revealed normal pressures in the pulmonary artery as well as in the chambers of the right side of the heart. The results of pulmonary function tests were almost completely within normal limits. The only abnormalities found were a slight increase in cardiac index and hyperventilation under all conditions of observation. However, bronchospirometry disclosed a marked limitation of gas exchange in the left lung, with carbon dioxide output limited to a lesser degree than oxygen consumption. These findings are consistent with the assumption that anastomoses from the bronchial artery result in a considerable blood flow through the pulmonary capillary bed of the left lung.

TABLE III
RESULTS OF CARDIOCIRCULATORY STUDIES

	Normal	Observed
Pressures in mm. of mercury		
Pulmonary artery, systolic	<30	23
Right ventricle, systolic	<30	24
Right auricle, mean	< 5	3
Cardiac index at rest (cardiac output, L./min./b.s. m^2)	3.05 + 0.6	4.23

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Book Reviews

Syphilis. Its Course and Management. By Evan W. Thomas, M.D., 317 pages. New York, 1949. The MacMillan Co.

Dr. Thomas, who as visiting physician to the Bellevue Hospital and director of the Rapid Treatment Center there holds an authoritative position in his field, has written this book chiefly "to give busy individuals a practical understanding of the principles underlying the modern diagnosis and treatment of syphilis." The text accordingly is concisely organized, explicit in the details of diagnosis and treatment and full of illustrative case material. The point of view is wholly oriented toward the modern era of penicillin therapy, based upon an experience at the Rapid Treatment Center of 12,000 patients treated with penicillin in various dosage schedules.

Of the sixteen chapters three deal with etiology, immunology and the clinical course of the untreated disease; one is reserved for a discussion of quantitative serologic tests for syphilis; one (by Dr. T. J. Bauer of the U.S.P.H.S.) on public health aspects; one (and a short one at that) on iodides, bismuth, arsenicals and fever therapy, and the remainder cover the problems of early infectious syphilis, latent syphilis, late benign syphilis, cardiovascular syphilis, neurosyphilis, syphilis and pregnancy and congenital syphilis and their treatment with penicillin. Treatment schedules in current use are stated clearly but their provisional nature is stressed.

The exposition is in simple, direct style, the type is clear and well spaced, making for easy readability. The whole constitutes a comprehensible and up-to-date volume suited to the needs not only of the specialist but also of the student and general practitioner whose responsibility for diagnosis and treatment of syphilis is greater in the antibiotic age than ever before.

A.B.G.

Understandable Psychiatry. By Leland E. Hinsie, M.D., 359 pages. New York, 1948. The Macmillan Company.

The title of Dr. Hinsie's book is self-explanatory as to what he set out to accomplish. His clear, delightful style of presentation has made a difficult subject "understandable" both to the medical profession and to the public. The material is well organized, modern and psycho-analytically oriented. The book should go a long way in taking the stigma out of psychiatry and psychiatric therapy. In Dr. Hinsie's attempt to simplify his subject matter he may have erred slightly on over-simplification, in that he symbolizes emotions, fears and anxieties a little too concretely. However, Dr. Hinsie has accomplished what he set out to do in a most pleasing manner.

S.M.D.

Coronary Heart Disease. By A. Carlton Ernstene, M.D., 86 pages. Springfield, Ill., 1948. Charles C. Thomas. *Price* $2.50.

Dr. A. Carlton Ernstene of the Cleveland Clinic has written a concise, lucid compendium of the problem and management of the various aspects of heart disease due to derangement of the coronary artery circulation. His division of the subject into its various clinical manifestations is a useful one. Such a division inevitably results in a certain amount of overlapping since the underlying disorder is essentially the same. That he has adroitly avoided repetition is evident from the fact that the entire book, exclusive of bibliography, consists of only eighty-six pages. It should prove of interest and value to student and practitioner alike.

J.B.

The Renal Origin of Hypertension.* Harry Goldblatt, M.D., 126 pages. Springfield, Ill., 1948. Charles C. Thomas. *Price* $2.75.

To Dr. Harry Goldblatt belongs the credit for proving that the kidney plays an important role in hypertension and for developing a successful method of producing this condition experimentally. His name has always been associated with carefully executed studies that have been amply confirmed.

Now, in monograph form, he has sum-

* Publication No. 14. In the American Lecture Series A Monograph in American Lectures of Pathology.

marized his investigations of the past two decades. These deal principally with the production of experimental renal hypertension by various means, the pathologic changes and mechanisms involved, the humoral mediators which participate and a brief summary of the similarities and differences between the experimental disease and its human equivalents.

Today there remain many unsolved problems concerning the part played by the kidney in hypertensive vascular disease and, indeed, serious doubts as to the function of renin and hypertensin as the humoral agents involved. There are no reservations about the major contributions of Dr. Goldblatt and the advance they have made to our knowledge. Lucidly written and attractively published, this volume is designed for those "whose interest is not sufficient to induce them to read the original papers or who do not have the time to devote to the reading of books on this subject." For this purpose it is an admirable addition to the many texts which have appeared on this important subject.

G.A.P.

General Endocrinology. By C. Donnell Turner, PH.D., 604 pages, Philadelphia, 1948. W. B. Saunders Co.

This textbook is designed primarily for college students with advanced biologic training although an effort is made to introduce correlations with clinical disease whenever possible. There is much in the way of fundamental information for the practitioner who wishes to acquire an anatomic and physiologic background. Unfortunately, the text suffers from the usual difficulty of being somewhat behind the times; as for example, in the discussion of antithyroid drugs and their mechanism of action and in the omission of the more recent work with purified pituitary hormones.

On the whole, the book makes good reading but is not to be taken as a clinical text.

S.C.W.

Festschrift zum 80 Geburtstag Max Neuberger's. Vol. II, Wiener Beiträge zur Geschichte der Medizin. Edited by Dr. Emanuel Berghoff. pp. 491. Vienna, 1948. Wilhelm Maudrich. *Price* $10.00.

This welcome volume is dedicated to Professor Max Neuberger, founder and head of the Vienna Institute for the History of Medicine and foremost medical historian of the day, upon the occasion of his eightieth birthday, December 8, 1948. The Festschrift is a collection of ninety-one essays on varied subjects of historical interest contributed by admirers, friends and former students, each choosing a topic of personal interest and writing in his own language. About one-third are in English, the remainder are chiefly in German and French. There are many quaint and interesting illustrations.

The essays are brief, some almost casual. Several deal with the etymology of certain medical terms, some with interesting medical personalities, places or manuscripts, some with episodes in the formulation of specialities, a few enter into philosophic considerations of historical development. All are interesting and enlightening, a tribute to Professor Neuberger's inspiration and influence. Even those who have no special interest in historical medicine will enjoy this volume for browsing and relaxation.

A.B.G.

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Volume VI

JANUARY TO JUNE

1949

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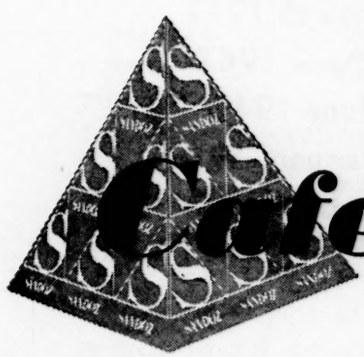

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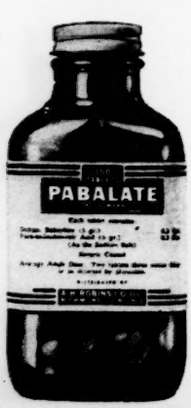

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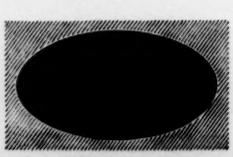

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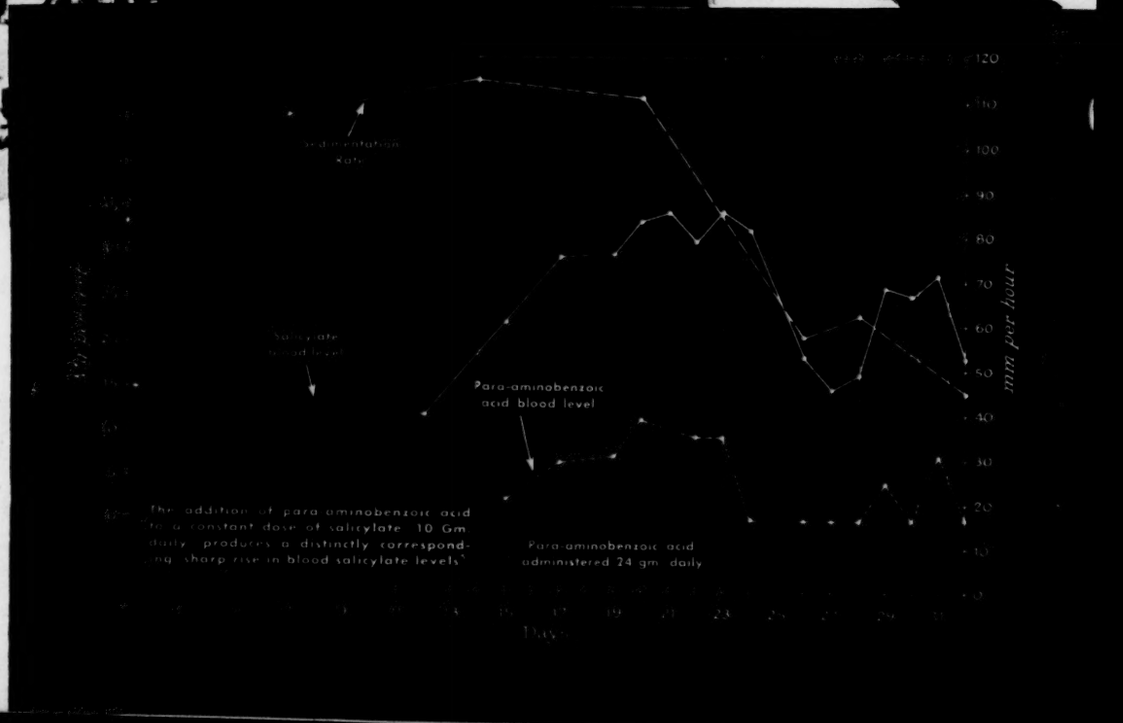

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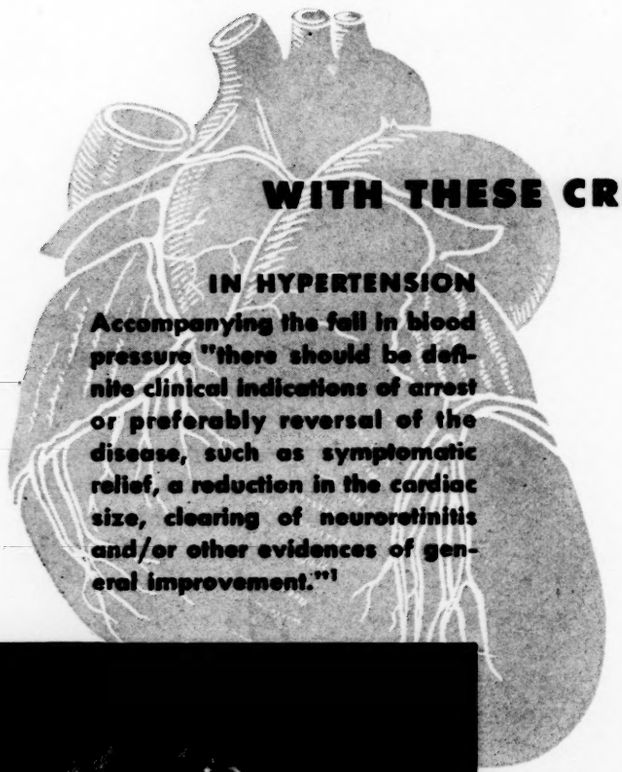

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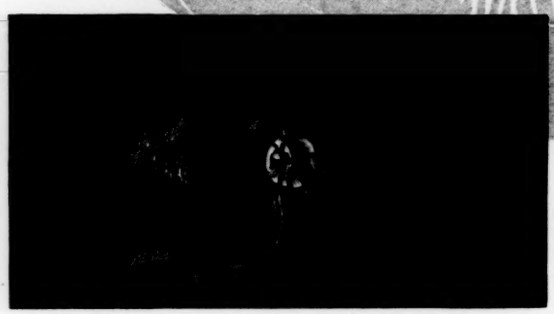

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CALORIES	676	VITAMIN A	3000 I.U.
PROTEIN	32 Gm.	VITAMIN B_1	1.16 mg.
FAT	32 Gm.	RIBOFLAVIN	2.0 mg.
CARBOHYDRATE	65 Gm.	NIACIN	6.8 mg.
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*Noble, R. L. (1946), Treatment of Experimental Motion Sickness in Humans, Canadian J. Research, Section E, 24:10.

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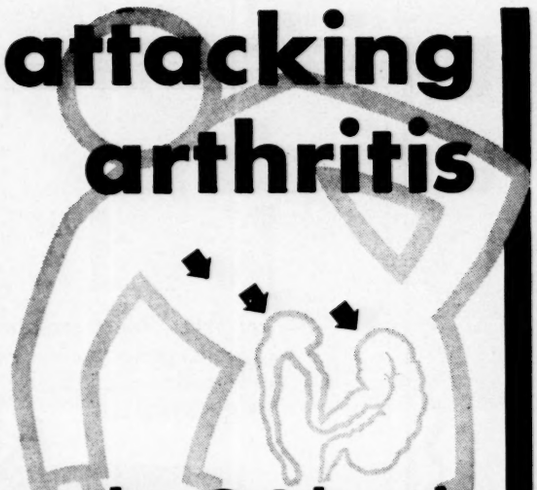

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*Nuzum, F. R.: In Diseases of the Digestive System, ed. by S. A. Portis, Lea & Febiger, 1944.

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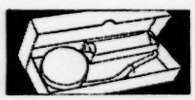

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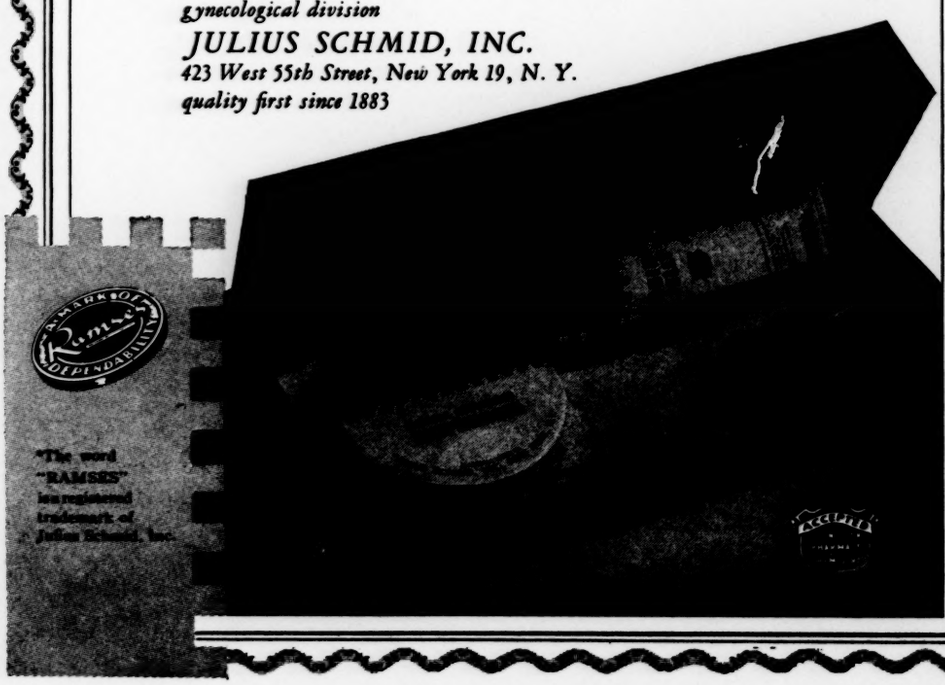

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Rakoff, A. E., Paschkis, K. E. and Cantarow, A.: A Clinical Evaluation of Dienestrol, A Synthetic Estrogen, J. Clin. Endocrinol., *7*:688 (Oct.) 1947.

"This low incidence of nausea [1.3 per cent] is . . . in contrast with that encountered during treatment with other synthetic estrogens."

Finkler, R. S. and Becker, S.: "A Preliminary Evaluation of Dienestrol in the Menopause, Am. J. Obst. & Gynec., *53*:513 (Mar.) 1947.

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Sikkema, S. H. and Sevringhaus, E. L.: Dienestrol: Another Synthetic Estrogen of Clinical Value, Am. J. Med., *2*:251 (Mar.) 1947.

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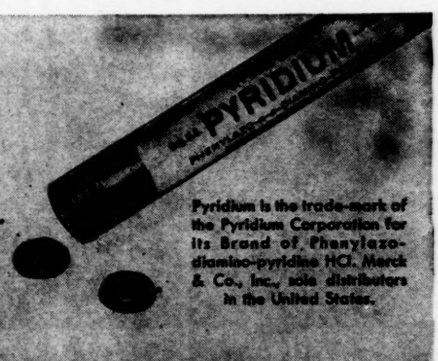

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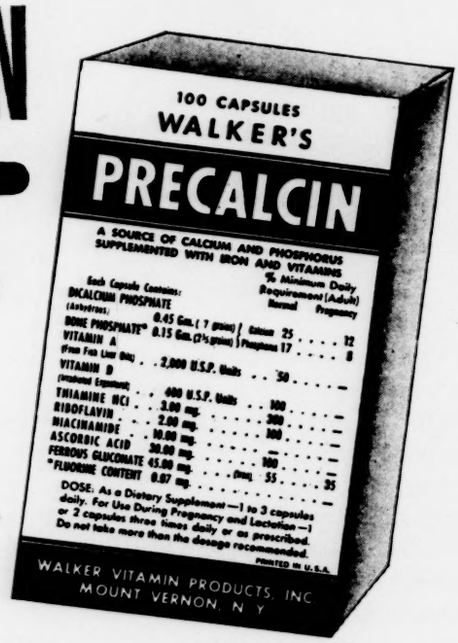
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